A Dissertation on

REMNANT CHOLESTEROL AS A RISK FACTOR FOR MYOCARDIAL INFARCTION IN AGE GROUP LESS THAN 40 YEARS

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DECLARATION

I solemnly declare that the dissertation titled ***"REMNANT CHOLESTEROL AS A RISK FACTOR FOR MYOCARDIAL INFARCTION IN AGE GROUP LESS THAN 40 YEARS"*** was done by me from July 2016 to June 2017 under the guidance and supervision of Professor **Dr. K.S.MANIAPPAN. M.D.,**

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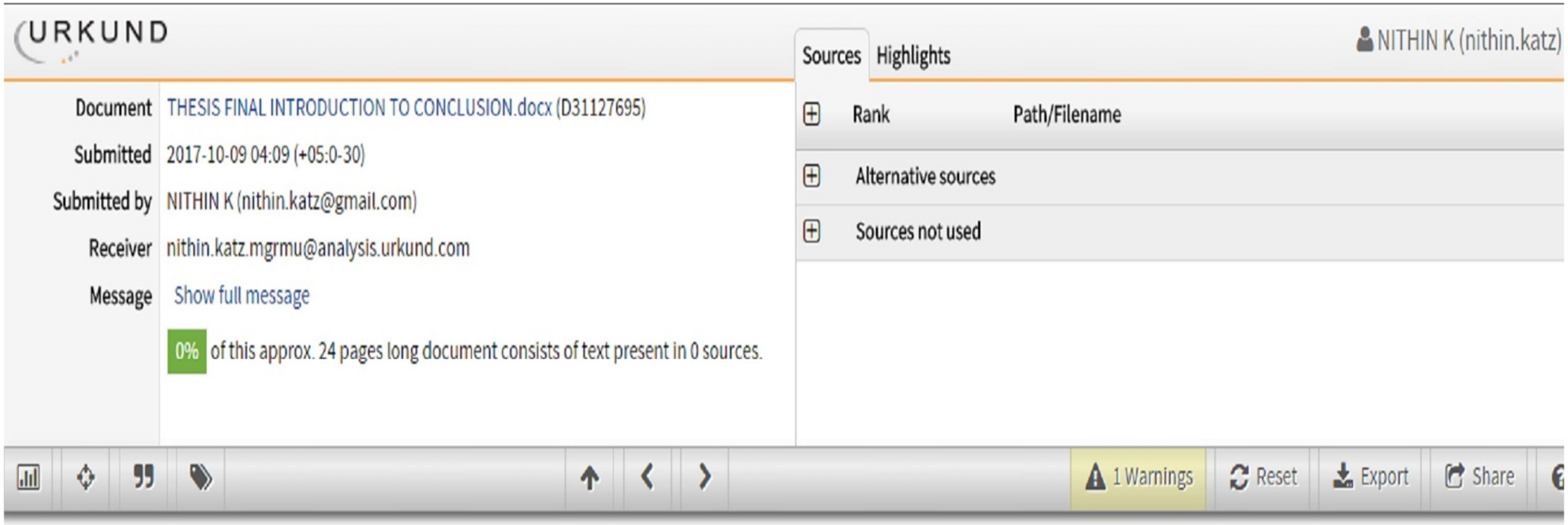

INTRODUCTION

Myocardial infarction accounts for the commonest cause of ICCU admission in coimbatore medical college and is one of the commonest cause of death globally and in India. Similar to the rising trend of non communicable diseases ,incidence of myocardial infarction also follows the same trend .Indian population with coronary artery disease shows higher incidence of hospitalisation ,morbidity and mortality compared to other ethnic groups. Myocardial infarction occurring before the age of 55 in men and 65 in women is called as premature myocardial infarction. The severe

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LIST OF ABBREVIATIONS USED

RC	-	Remnant Cholesterol
LDL	-	Low Density Lipoprotein
HDL	-	High Density Lipoprotein
VLDL	-	Very Low Density Lipoprotein
IDL	-	Intermediate Density Lipoprotein
TG	-	Triglycerides
MI	-	Myocardial Infarction
CE	-	Cholesteryl Esters
PL	-	Phospholipid
Apo	-	Apolipoprotein
NEFA	-	Non Esterified Fatty Acids
MTP	-	Microsomal Triglyceride Transfer Protein
LPL	-	Lipoprotein Lipase
HTG	-	Hypertriglyceridemia
CETP	-	Cholesteryl Ester Transfer Protein
ABCA1	-	Adenosine Triphosphate–Binding Cassette A1
RCT	-	Reverse Cholesterol Transport
SRB1	-	Scavenger receptor class B type I
VCAM	-	Vascular Cell Adhesion Molecule
CAD	-	Coronary Artery Disease
ox-LDL	-	Oxidized LDL
STEMI	-	ST Elevation Myocardial Infarction
PCI	-	Percutaneous Coronary Intervention

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INTRODUCTION

Myocardial infarction accounts for the commonest cause of ICCU admission in coimbatore medical college and is one of the commonest cause of death globally and in India. Similar to the rising trend of non communicable diseases ,incidence of myocardial infarction also follows the same trend .Indian population with coronary artery disease shows higher incidence of hospitalisation ,morbidity and mortality compared to other ethnic groups. Myocardial infarction occurring before the age of 55 in men and 65 in women is called as premature myocardial infarction. The severe form is defined as coronary artery disease occurring below the age of 40 years .The risk factor profile of myocardial infarction in young includes higher smoking rates, more family histories of coronary heart disease, and a lipid phenotype that is characterized by a predominance of elevated triglyceride-rich lipoproteins. Coronary artery disease affects Indian population 5-10 years younger than other communities and the lesions are more severe and diffuse. Remnant cholesterol is defined as the cholesterol fraction in triglyceride-rich remnant lipoproteins. Remnant cholesterol consists of very low–density lipoproteins (VLDL) and intermediate density lipoproteins (IDL) in the fasting state and of VLDL, IDL, and cholesterol

present in chylomicrons in the non-fasting state. Elevated levels of remnant cholesterol have been associated with increased cardiovascular risk. Myocardial infarction in young individuals (≤40 years) has a typical risk factor profile and a lipid phenotype which is characterized by a predominance of elevated triglyceride-rich lipoproteins. The casual association between atherogenesis and myocardial infarction is established but the establishment of association between premature myocardial infarction and remnant cholesterol will throw light to the need of aggressive lipid lowering therapy in young age group.

AIMS AND OBJECTIVES

Aim

The aim of my study is to investigate the role of remnant cholesterol in patients with STEMI of age less than 40 years.

Objectives

- To identify the causal association between elevated levels of remnant cholesterol and myocardial infarction in age less than 40 years.

REVIEW OF LITERATURE

LIPIDS – HISTORICAL ASPECTS

The effects of dietary fat on body and mind is mentioned in Indian literature dating back to 3500 BC. These details regarding its implications on human body in Bhagavat Gita is regarded as the oldest record available till date on phenotype and diet[1].Similar concepts regarding dietary fat and human body changes existed in Biblical times[2] .

In the year 1784 pure cholesterol was extracted from gall stones by French chemist and physician Francois Pelletier[3].But the extracted molecule was given the name cholesterin by Michel E.Chevreul , a chemist from France[4].It took nearly a hundred years to get the knowledge about the molecular formula of cholesterol. In the year 1888 Austrian botanist Friedrich Reinitzer gave insights to the world that cholesterol molecule was made up of a tetracyclic skeleton and four rings[5].Two scientists Heinrich O.Wieland and Adolf Windaus was consecutively awarded Noble Prize in chemistry in years 1927 and 1928 for their description regarding the structure of cholesterol[6].The genetic connections between cholesterol and heart attacks was described in the year 1939 by a Norwegian clinician Carl Muller[7].In 1985 Michael S Brown and Joseph L Goldstein jointly received Nobel Prize for their

contribution in the discovery of metabolism of cholesterol and research activities regarding treating options for diseases caused by abnormally elevated cholesterol[8].Dr D S Fredrickson is the father of lipidology and identified various apolipoproteins[9] and identified cholesteryl ester storage diseases and Tangier disease.

The physician scientist from France Michel Macheboeuf is regarded as the father of plasma lipoproteins for his demonstration of association between lipids and proteins ìlipido-protéidiquesî[10].The first insights about the relationship between cholesterol and atherosclerosis was given by Windaus in the year 1910[11].This was based on his observation that plaques from aortas of humans with evidence of atherosclerosis had 20 fold concentration of cholesterol than normal aortas. The connection between cholesterol and coronaries was discovered in 1950 when John Gofman mentioned elevated cholesterol levels ,low –density lipoprotein(LDL) levels as a cause of myocardial infarction(MI).He also discovered that individuals with elevated high-density lipoproteins(HDL),there is a less likelihood of an MI. The cholesterol biosynthesis pathways were described by four scientists – Feodor Lynen, George Popjak, John Cornforth and Konard E Bloch. Coronary thrombosis as a cause of acute MI as described by James B Herrick in the year 1912 .

PROPERTIES AND COMPOSITION OF LIPOPROTEINS

The lipoproteins of plasma consist of polar lipids, neutral lipids and apolipoproteins which are specialized proteins. The neutral lipids of plasma are cholesteryl esters (CE) and Triglycerides(TG), phosphatidylcholine , phosphatidylethanolamine ,free cholesterol, other phospholipids and sphingomyelin constituting the polar lipid component. The size and structure of lipoproteins determine their composition .The content of neutral lipid is the main determinant of its size and density, the least dense particle having the largest lipoprotein and has highest neutral to polar lipid ratio. The amount of charged lipids and conformation of apolipoproteins determines the surface charge .

TABLE 1 PLASMA LIPOPROTEIN PROPERTIES

CLASS	D (nm)	d (gm/ml)	Mobility	TG	CE	FC	PL	Pro	MAJOR APOS
Chylomicron	80-500	<0.93	α2	86	3	2	7	2	B-48, E, A-I,A-II, A-IV, C
VLDL	30-80	0.95-1.006	Pre-β	55	12	7	18	8	B-100, C-I, C-II, C-III, E
IDL	25-35	1.006-1.019	Slow pre-β	23	29	9	19	19	B-100, E
LDL	21.6	1.019-1.063	β	6	42	8	22	22	B-100
HDL_2	10	1.063-1.125	α	5	17	5	33	40	A-I, A-II
HDL_3	7.5	1.125-1.210	α	3	13	4	25	55	A-I, A-II
Lp(a)	30	1.055-1.085	Slow pre-β	3	33	9	22	33	B-100, apo(a)

d, density; D, diameter; FC, free cholesterol; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); PL, phospholipid; Pro, protein; TG, triglyceride; VLDL, very-low-density lipoprotein.

APOLIPOPROTEINS

Apo lipoprotein distribution in lipoproteins is a major determinant of their metabolic effects. They are classified into soluble and insoluble types .Soluble apolipoproteins comes under same family of genes with terminal exon IV coding for the apo region ,which in turn is responsible for the unique biological properties. Soluble apolipoproteins can be exchanged and amphipathic helical regions which in turn mediate the binding to the surface of lipids. Lecithin cholesterol acyltransferase mediated cholesterol esterification is mediated by apo C-1and apo A-1[12,13].Hydrolysis of VLDL and chylomicrons by lipoprotein lipase is activated by apo C-11[14,15].The ligand mediating uptake of remnant chylomicrons and IDL is apoE[16-18].Plasma TG levels and apoC- III levels correlates with each other[19,20].Apo A- V which occurs in very low levels in plasma has antilipemic properties[21]. The major protein in IDL,VLDL and LDL is apoB-100,which in turn has ligands which mediate cellular uptake of LDL by LDL receptor. Apo B-48 is a form of apoB which is truncated and is present in chylomicrons .Apo B-48 is produced by mRNA editing wherein a coding amino acid codon is changed to a stop codon ,the resultant product of gene expression lacking the binding domain for LDL receptor[22,23].

LIPOPROTEIN PRODUCTION

Triglyceride –Rich Lipoproteins

VLDL assembly and secretion is mediated by hepatocytes and is driven by TG synthesis from endogenous fatty acids, chylomicron assembly and secretion is mediated by enterocytes in the intestine and is driven by TG synthesis from exogenous fatty acids .Elevation of VLDL, chylomicrons or both leads to hypertriglyceridemia.TG concentration during fasting is determined by the concentration of non esterified fatty acids(NEFA) which is available for uptake in hepatocytes. Following an oral fat intake ,chylomicron hydrolysis liberates NEFAs which are used for VLDL-TG secretion and production in hepatocytes. VLDL assembly in hepatocytes is described by a two step model. Microsomal triglyceride transfer protein(MTP) in rough endoplasmic reticulum lumen does partial lipidation of apoB with TG ,cholesteryl esters. This process gives rise to a pre-VLDL which is associated weakly with membrane of endoplasmic reticulum and interacts with TG rich particle in smooth ER. Insulin resistance raises the plasma NEFAs and impairs storage of fatty acids used for the production of VLDL.This is responsible for the fasting hypertriglyceridemia and postprandial lipemia in insulin resistant states

and diabetes mellitus. This in turn is a contributor to complex phenotype in diabetes linked to obesity and in metabolic syndrome(MetS).

Intermediate And Low Density Lipoproteins

VLDLs are modified following their entry into plasma by lipoprotein lipase(LPL). VLDL contains apos B-100, E, C-I, C-II, and C-III and is the major carrier of endogenous TG.LPL has association with capillary proteoglycans and the peripheral tissues that are perfused via the capillary bed is the main site for the uptake of the fatty acids released by LPL. LPL activity was stimulated by apoC-II was discovered by Havel and LaRosa. LPL action on VLDLs hydrolyses VLDL to IDLs and LPL hydrolyses chylomicrons to chylomicron remnants. Deficiency of LPL and ApoC-II are associated with severe form of HTG. There is strong association with moderate HTG and type 2 diabetes and atherosclerosis. During VLDL hydrolysis by LPL, the C apos, including apoC-II,are transferred to HDL, producing IDL and the activity of LPL is stopped, because IDL is not a substrate for LPL . Hepatic lipase(HL) do not require apoC-II, and hydrolyze IDL to LDL which is the product containing mature apoB-100–. Most of the apoE is lost during this step. During the postprandial state HL remodels HDL through PLs and TGs hydrolysis.

High-Density Lipoproteins

Models detailing the production, structure, remodelling, and catabolism of HDLs were more difficult to identify than those of the lipoproteins containing apoB. HDLs are small in size and heterogeneous in composition ; so the conventional methods like x-ray crystallography, cryo electron microscopy, and nuclear magnetic resonance imaging have very limited value. Turnover of HDL cannot be studied by traditional kinetic methods as all the HDL components are exchangeable.

HDLs are heterogeneous in nature and are classified based on their electrophoretic mobility, size, and density. HDLs are separated by two-dimensional gel electrophoresis, on the basis of both electrophoretic mobility and size. HDLs are also classified based on the presence of apoA-II. Most of the particles contains apoA-I and apoA-II (LpA-I/A-II) but some has only apoA-I (LpA-I). LpA-I/LpA-II formation in plasma is by fusion of nascent discoid apoA-II HDL with small spherical LpA-I which is LCAT mediated or by a mechanism in which more lipophilic apoA-II displaces apoA-I . ApoE, which is a minor HDL protein, associates preferentially with large HDL. The HDL apolipoproteins distributions having exchangeable properties , undergo modification by phospholipid transfer protein (PLTP), LCAT, HL and cholesteryl ester

transfer protein (CETP). Remodelling of HDL structure and dissociation of apoA-I are very much essential in functions of HDL including reverse cholesterol transport (RCT). The site of apos synthesis and lipidation is in the ER. Further lipidation in the Golgi apparatus occurs after ER following which 50% of apoA-I is secreted on small nascent HDL, and the remaining part is secreted free of lipids. ApoA-II is intracellularly lipidated rapidly, this process catalyzes the dimerization of the particle , leading to its secretion as a dimer associated with lipids on nascent HDL particles which lacks apoA-I. The fusion between apoA-II nascent HDL with small spherical apoA-I HDL is catalyzed by LCAT the final end product being LpA-I/A-II spherical HDL. Golgi apparatus ApoE is associated with VLDL particles which is maturing. ApoE in VLDL is remodelled rapidly into particles of LDL-size and is transferred to HDL, on HDL it forms homo and heterodimers with apoA-II. The lipoproteins which are secreted undergo retro endocytosis sometimes, leading to transfer of apoA-I and apoA-II to LDL-sized particles, apoE is re secreted following its transfers to HDL. Interaction between ApoA-I , adenosine triphosphate–binding cassette A1 (ABCA1) transporter and its associated membrane lipids yields nascent HDL as end product.

Lipoprotein Remodeling And Catabolism

Reverse Cholesterol Transport

Extrahepatic tissues can synthesize but lacks the mechanism to degrade cholesterol. Accumulation of cholesterol in macrophages which is an important cell type in atherogenesis, produces a pathologic lipotoxic state. The mechanism for the disposal of cholesterol in extrahepatic tissues is RCT wherein HDL is the key player.

There are three steps in RCT: (1) efflux of cholesterol from monocyte-derived macrophages within the wall of arteries, (2) interaction and esterification with lipid transfer proteins in the plasma compartment (3) selective uptake of HDL-CE by its receptor in liver.

Lipoprotein handling by the body is referred to as the lipoprotein particle metabolism .It has two pathways endogenous pathway and exogenous pathway .This based on whether the lipoprotein is chiefly composed of dietary lipids wherein they are metabolised by exogenous pathway and those originating from liver through de novo synthesis are metabolised by the endogenous pathway.

Exogenous Pathway

Fats in the chime is emulsified by bile following which pancreatic lipase cleaves the triacylglycerol molecule to 2-monoacylglycerol and two fatty acids .This is readily absorbed by the enterocytes from the chymus .The fatty acids and monoacylglycerides are transformed again into triglycerides inside the enterocytes. The resultant triacylglycerols ,phospholipids,cholesterol and cholestyryl esters are assembled with apolipoprotein B-48 to form nascent chylomicron.The nascent chylomicron is secreted into the lacteals by a apolipoprotein B-48 dependent process. These nascent chylomicrons bypass the hepatic circulation and are drained into bloodstream by the thoracic duct.

Nascent chylomicrons in the blood interacts with HDL particle ,during which apolipoprotein C-11 and apolipoprotein E are donated by HDL particles to the nascent chylomicron. Chylomicron is considered mature after this step. Lipoprotein lipase in the endothelial lining of blood vessels is activated by apoC-11.Lipoprotein lipase mediates the hydrolysis of of triacylglycerol and releases fatty acids and glycerol from the mature chylomicron. This released fatty acids and glycerol is absorbed in the peripheral tissues for energy and storage.

The mature chylomicron hydrolysis by lipoprotein lipase results in the formation of chylomicron remnant. This remnant chylomicron is circulated in the bloodstream following which it interacts with the chylomicron remnant receptor which is mainly found in the liver via its interactions with the apo E particle. This interaction leads to the endocytosis of remnant chylomicron following which it is hydrolyzed in the lysosomes. The end product of lysosomal hydrolysis are fatty acids and glycerol which is used for energy or stored for later use inside the cell

Exogenous Pathway

The central platform for handling lipids is the liver because of its ability to store glycerol and fats in the hepatocytes. Hepatocytes also have the ability for de novo synthesis of triacylglycerol, a nd also synthesize bile from cholesterol.

ApoliproteinB-100 causes assembly of triacylglycerols and cholesteryl esters in the hepatocytes to form nascent VLDL particle, following which it is released into the blood stream by an apoB-100 dependant process.

Circulating VLDL particles on reaching the endothelial cells activate LPL via apo C11.This cause VLDL hydrolysis and releases fatty

acids and glycerols. The released glycerol and fatty acids are absorbed by the muscle and adipose tissue. The resultant VLDL particle after hydrolysis is called as the VLDL remnant or as the intermediate density lipoprotein(IDL).The circulating remnant VLDL is absorbed by the liver by its interaction between the remnant receptor and apoE.

The VLDL remnant undergoes hydrolysis by the hepatic lipase releasing fatty acids glycerols and IDL remnants called as the low density lipoproteins. LDLs have a relatively higher cholesterol content LDL is circulated and is absorbed in liver and peripheral cells by its interaction between LDL receptor and ApoB-100 on the LDL particle .The mechanism of absorption is by endocytosis and the internalised particle undergoes hydrolysis within lysosomes releasing cholesterol.

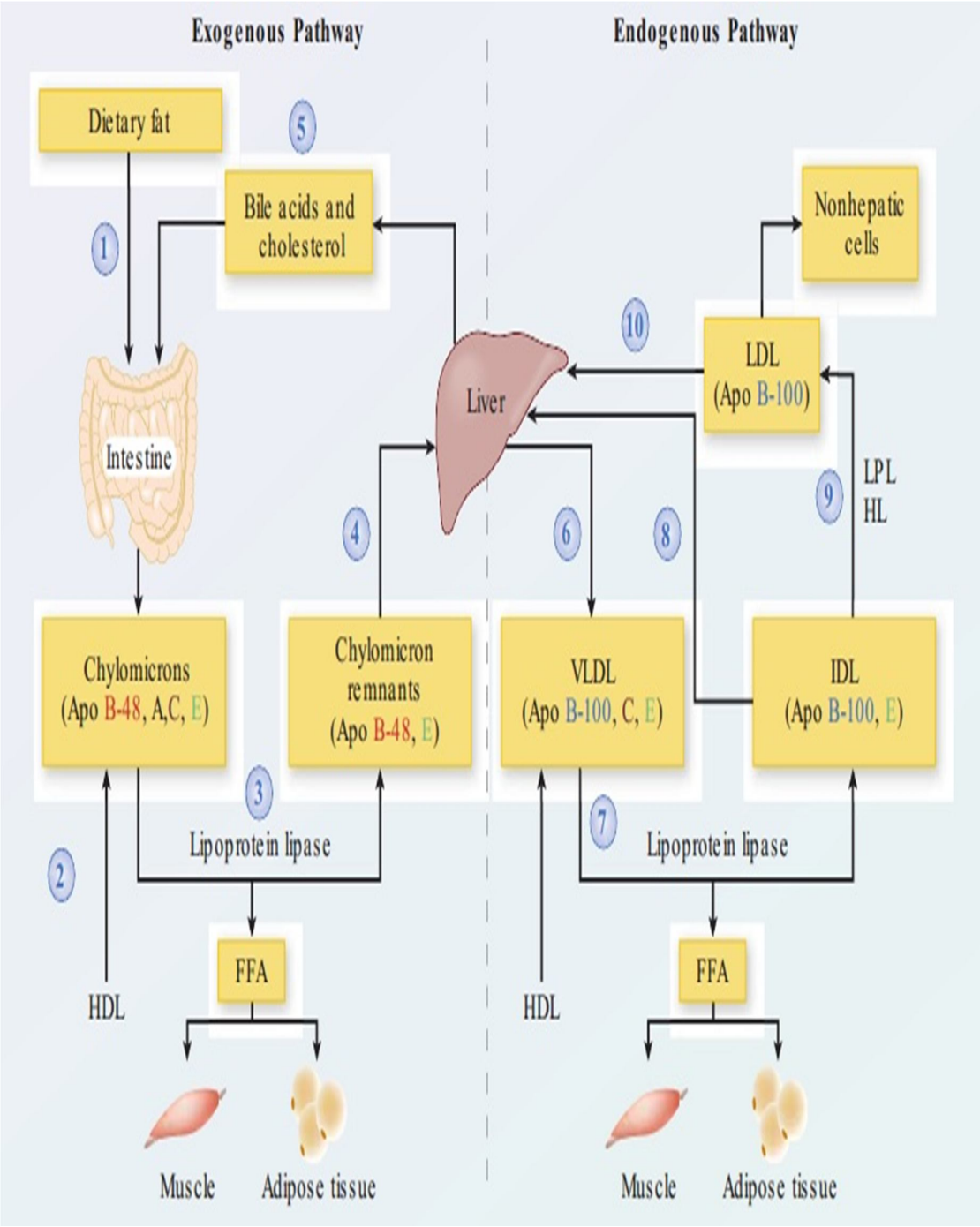


Figure 1 The lipoprotein transport system.

LIPOPROTEINS AND ATHEROGENESIS

Much attention on pathophysiology of atherosclerosis is centred on LDL due to the evidence which supports the causal role for LDL. LDL accumulates in the artery wall when it is excess. Increased endothelial monolayer permeability accounts for LDL accumulation at areas which are prone formation of lesion. Localization of the regions predisposed to lesion formation and increased accumulation of Evans blue, a dye which has property of binding to albumin, and when found in the intima, is an indicator of permeability to proteins. Increased LDL retention in intima in the studies which used trapped ligand is the important contributory factor for its accumulation. Lipoprotein particle entanglement with macromolecules of extracellular matrix was seen in the intima of arteriole of animals which took a diet which was atherogenic. These observations gave a clue that retention of lipoprotein particles in atherosclerotic intima is by their binding to extracellular matrix . The interaction between LDL particles and constituents of the extracellular matrix of arteries has been detailed biochemically. The interaction between LDL particles and proteoglycan is influenced by a specific site in the apoB sequence in a critical manner . Proteoglycan constituents of the extracellular matrix of arteries are chondroitin sulfate–rich appear to retard LDL. Retention of the apoB– containing particles in the arterial

intima is mediated by Biglycan and versican . These chondroitin sulphate proteoglycans in excess amount appears to play a primordial role in the pathogenesis of atherosclerosis. The smooth muscle cells that are subjected to cyclic strain showed increased production of proteoglycan molecules. Response to biomechanical stimuli in an altered manner by smooth muscle cells promote the intimal extracellular matrix generation providing a fertile field for atherosclerosis initiation .

Due to different properties of various LDL fractions ,they interact with extracellular matrix differentially. The small dense LDL fraction binds to proteoglycan and undergo glycation more than the larger“fluffier” fraction. Individuals with high triglycerides and low levels of HDL, have more small dense LDL particles accumulation in which are characteristics of the metabolic syndrome and diabetic dyslipidemia. The link between increased retention of small dense LDL and these conditions gives insights for the increased propensity of these components in promoting atherosclerosis. These aspects of LDL help us in understanding the reason why diabetes is so intensely atherogenic in spite of near-average or average levels of LDL cholesterol. Accessory enzymes also promotes the retention of LDL particles in the intima additionally to the well defined interactions between intimal extracellular matrix and LDL species .Lipoprotein lipase acts as a bridge between

LDL particles and the extracellular matrix through a non enzymatic mechanism. Macrophages has the ability to synthesize lipoprotein lipase in the wall of the arteries. Microvascular endothelial lipoprotein lipase halts atherogenesis but the effect of local lipoprotein lipase in intima may promotes LDL retention intensifying atherogenesis. Increased LDL particles binding to proteoglycans of intima is enhanced by secretory phospholipases which are over expressed within atheromata . Secreted form of sphingomyelinase augment the aggregation of lipoprotein particles in the artery wall, and also promotes the . Increased binding of LDL particles to proteoglycan is also mediated by sphingomyelinase .There are a lot of factors promoting LDL accumulation in the intima at sites of early atherogenesis. Sequence-specific interactions of LDL fractions with chondroitin sulfate–rich proteoglycan in the intima, which are augmented by the action of accessory enzymes conspires to trap lipoproteins in the intima and increases their residence time**.** Increased dwelling of LDL for prolonged time in the areas of the intima which are more prone for atherosclerosis leads to a greater oxidative modification of these particles , and also are excluded from protection provided by antioxidants .All these triggers various pro-oxidant mechanisms leading to modification of the lipoprotein particles which are trapped for longer periods in the vascular intima due to their binding to proteoglycans.

Erythrocytes are extravasated from microvessels which are disrupted in lesions which are more advanced leading to deposition of heme which is an iron source which catalyzes the reaction by fenton chemistry in the extracellular space. As a result of proteoglycan binding delaying the transit of lipoproteins enzymes myeloperoxidase and phospholipases have an increased opportunity for lipoprotein modification . The production of oxidized phospholipids by this mechanism leading to production of biologically active species that are capable of eliciting an inflammatory response in the intrinsic vascular wall cells and leukocytes. The link between, lipoprotein particle accumulation in early atherosclerotic lesion and pro inflammatory reactions which amplify and sustain the process of atherosclerosis is the response to retention of particles in the vessel wall.

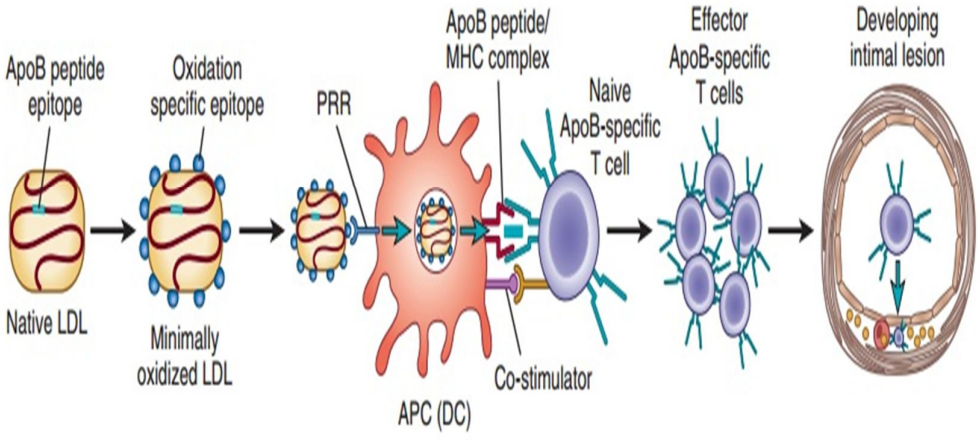


Figure 2 Role for LDL as an antigen promoting atherosclerosis

The significance of the oxidation hypothesis in real life scenario is uncertain . Many trials have showed a failure of antioxidant vitamins, small molecules, and soluble and lipoprotein-associated phospholipases inhibitors to reduce cardiovascular events. A humoral immune response is generated by which antibodies to oxidation-specific epitopes on LDL generate atheroprotective oxidized LDL. This molecule may be the by B1 lymphocytes secreted immunoglobulin-M antibodies which attenuated atherosclerosis in experimental conditions. These raised a new prospect to limit atherogenesis by vaccination with modified-LDL-derived antigens . Native LDL activates the adaptive immune response by T-cell. The ability to elicit a T-cell response is impaired in mice following progressive LDL oxidation. Native LDL stimulating T-cell activation reflects in tolerance break . Activated T cells in atherosclerotic lesions secrete Th1 cytokines promote atherosclerosis in experimental set up , as opposed to anti oxidized LDL antibodies offering protection to atherosclerosis

THE ROLE OF HIGH-DENSITY LIPOPROTEIN AS AN ANTIATHEROGENIC LIPOPROTEIN

HDL is regarded as an inverse risk factor for atherosclerosis in many epidemiologic evidence based studies . The role of HDL in reverse

cholesterol transport was first hypothesized by Glomset . The mechanism of HDL mediated cholesterol egress from foam cells which are lipid laden is only recently understood. The mediator of transfer of cholesterol to nascent HDL particles is ABCA1 , ABCG1particle transfers cholesterol in from cells to mature HDL elements . The cholesterol uptake from HDL by liver and steroidogenic organs is mediated by Scavenger receptor class B type I (SR-BI) . The role of HDL in lipid accumulation in macrophage is seen in Genetic disorders in humans like Tangier disease caused by mutations . Various experiments done in vitro conditions details the HDL fractions ability to mediate the efflux of lipids from cells that are cholesterol-loaded. In persons with low plasma HDL levels there is an impaired reverse cholesterol transport that contribute to the increased cardiovascular risk .Apart from the role of HDL in cholesterol shuttling, HDL has impact on normal biology of arteries as the carrier of antioxidant and anti inflammatory proteins. Catabolism of biologically active and pro inflammatory oxidized phospholipids associated with modified LDL particles is done by phospholipases associated with the HDL. Association of antioxidant proteins that are putative like Platelet-activating factor acetyl-hydrolase and paraoxonase-1 with HDL particles were established by proteomic studies associated with HDL particles, these studies also delineated a

number of other proteins that alter arterial biology favourably. Association between HDL particles and complement regulatory proteins and protease inhibitors is documented . The anti inflammatory role of HDL is shown in the In vivo experiments done in animals. An example for this is the vascular cell adhesion molecule (VCAM) in expression injured arteries limited by HDL infusions. All of the HDL particles do not have anti inflammatory actions. There are postulates regarding the existence of HDL species that are pro inflammatory in nature . Serum amyloid A which is an acute phase reactant is increased 10- to 100-fold during a systemic inflammatory state during the acute-phase response to infection or tissue injury ,like that of C-reactive protein. The serum amyloid A which is an acute-phase reactant with amphipathic nature binds to HDL and displaces protein that are atheroprotective in nature from HDL particles. This the cause of HDL losing its anti inflammatory properties, during stages of acute inflammation. There are some in vitro assays which suggested that , HDL promotes inflammation. There is an inverse relationship between HDL and cardiovascular disease but details regarding decreasing atherosclerosis by HDL manipulation is still hypothetical. Agents causing increase HDL like cholesteryl ester transfer protein inhibitors, extended release niacin, and fenofibrate didn’t show a decrease in the cardiovascular events.

Genetic And Familial Disorders Of Lipoprotein Metabolism.

Abnormal synthesis ,processing and catabolism of lipoprotein particles in the plasma results in the lipoprotein disorders. About 50% of the patients of age less than 60 years who have confirmed coronary artery disease by angiography have familial lipoprotein disorders..The incidence of lipoprotein disorders at first myocardial infarction is more in younger age group and incidence decreases with increasing age .In patients with severe hyperlipidemia with total cholesterol more than 300mg/dl and triglycerides more than 500 the possibility of a genetic disorder is to be evaluated .The presence of xanthomas always signal an underlying genetic defect. Lipoprotein disorders are basically divided into four:- elevated LDL cholesterol , reduced HDL cholesterol, with increased triglycerides and VLDL, elevated levels of remnant chylomicrons and IDLs ,elevated levels of lipoprotein a particle.

Table 2 Genetic factors in Lipoprotein abnormalities

Lipoprotein Profile	Genes Implicated
Increased LDL cholesterol	Apolipoprotein B
	Apolipoprotein E
	LDL receptor
	Lysosomal acid lipase
Decreased HDL cholesterol	Apolipoprotein AI
Increased trigyceride	ApolipoproteinCII
	Apolipoprotein CIII
	Lecithin cholesterol acyltransferase
	Lipoprotein lipase
Increased remnants and LDL	Apolipoprotein E
Increased Lipoprotein (a)	Apolipoprotein (a)

Elevated LDL Cholesterol

There is a three fold increase in ischemic heart disease related deaths in men who have cholesterol levels more than 240mg/dl when compared to individuals with cholesterol more than 240mg/dl. The risk gradient increases with increasing cholesterol levels .Elevated cholesterol levels is a reflection of elevated LDL cholesterol as 70% of plasma cholesterol is constituted by LDL .Patients with elevated serum

cholesterol alone are classified into Fredrickson type IIa hyperlipoproteinemia.

LDL cholesterol levels are affected by a number of genetic conditions. The most common among them is Familial hypercholesterolemia and is documented in approximately 5% of the population with MI. This occurs due to a defect in LDL receptor gene present on chromosome 19. Patients who inherit defective genes from both parents are affected severely due to gene dosage effect. The defect in LDL receptor causes LDL catabolism is impaired, resulting in an enhanced conversion of IDL to LDL due to the resultant impaired receptor mediated IDL uptake. Homozygotes of familial hypercholesterolemia have a six times elevation in LDL cholesterol whereas heterozygotes have twice the normal level. Homozygotes have typically total cholesterol levels of 650 to 1000mg/dl and have elevated cholesterol in the umbilical blood. Typical cases have planar cutaneous xanthomas at birth and most of them suffer from a fatal myocardial infarction by the age of 30 years .Patients also have xanthomatous aortic sclerosis which may present as recurrent syncope .Heterozygotes usually present late and only 5% will have MI by 30 .They have nodular tendon xanthomas of achelis and other tendons. Patients usually have a slender physique and are usually not associated with diabetes or hypertension.

Drug therapy with HMG coA reductase inhibitors is necessary which lower the cholesterol synthesis and increasing LDL receptor synthesis .Homozygotes may require gene therapy plasma exchange or liver transplantation..

Another relatively common disorder causing LDL cholesterol elevation is the familial defective apo B100.This occurs due to the mutation in the apoB gene located on chromosome 2.This leads to impaired binding to the LDL receptor resulting in an impaired LDL uptake.

Apo E genetic variations cause 3-5% of LDL level alterations. Gene for apo E is located on chromosome 19 which also codes for apoCI and CII. There are 3 alleles for apoE in the population E2,E3and E4.E3/3 genotype is the most common genotype and E4/3, E3/2genotypes have mean LDL cholesterol higher and lower by 10mg/dl respectively.E3/2 genotype is associate with lower atherosclerosis incidence when compared to other genotypes.

The most common genetic hypercholesterolemia is familial combined hyperlipidemia. It has an unknown cause is one of the most common cause of premature coronary artery disease..It is characterized by LDL ,VLDL and triglyceride cholesterol elevation. There is an

overproduction of VLDL and apoB in familial combined hyperlipidemia leading to hypertriglyceridemia and elevated plasma VLDL in some subjects and other patients with an efficient lipolysis have an elevated LDL. There is a strong family history of premature CAD in the patients .Other lifestyle disorders like diabetes ,obesity alcohol, estrogens exogenously and hypothyroidism have an enhanced effect on this.

There is an elevated apoB levels in approximately 33% of the patients with premature CAD .Patients with elevated apo B with hypertriglyceridemia or CAD usually require aggressive treatment. Some patients with familial combined hyperlipidemia will have a small dense LDL .Patients with small dense LDL will have elevated apoB decreased HDL and increased triglycerides .Small dense LDL are highly atherogenic due to its higher susceptibility to oxidation .

Elevated TGs And Reduced HDL Cholesterol

Many studies have shown that a reduced HDL cholesterol level less than 35mg/dl is an independent risk factor for CAD. There is a strong correlation between apoAI levels and HDL cholesterol levels. The apoAI fractional catabolic rate is the determinant of the differences in HDL and apoA1 levels among individuals. With the decrease in particle size the

catabolic rate increases which leads to elevated triglycerides which in turn caused decreased HDL.

Individuals with apoA1chromosome mutation on chromosome 11 will have a defective HDL production .These individuals are at high risk of developing premature CAD and will have planar xanthomas .LCAT mutation due to genetic mutation chromosome 16 will have inability to esterify free cholesterol resulting in deposition of cholesterol in tissues and there will be abnormal lipoproteins of all types .People with Tangiers disease will have both an abnormal and rapid HDL clearance. There will be apoA1 substitution causing dyslipidemia and LPL deficiency.

Two enzyme deficiencies have abnormally elevated HDL cholesterol levels .Hepatic lipase deficiency due to hepatic lipase gene mutation on chromosome 15.This causes a block in the remodelling of HDL_2 to HDL_3 and have elevated HDL despite which patients are at high risk of premature CAD. Mutation of the CETP gene on chromosome 16 causes CETP deficiency. This causes elevated apoA1 and HDL levels and have a decreased apoB and LDL cholesterol levels.

Association between high triglycerides and low HDL cholesterol is seen in many patients is supposed to be casually linked. Approximately 25% of the patients with premature CAD have hyper triglyceridemia.

Patients with diabetes mellitus hyper triglceridemia constitutes to be a CAD risk factor. The genetic basis of familial hyper triglyceridemias is mostly unknown and is a genetically heterogeneous disorder. Disorder with strong association of hyper triglyceridemia with hyper insulinemia hyperglycemia and hypertension is labelled as syndrome X. Hyper triglyceridemias may be due to an impaired catabolism or an increased production of VLDL. In presence of exacerbating factors a genetic defect in catabolism of VLDL is expressed. VLDL overproduction is seen in obesity, diabetes ,alcohol, estrogen use and are unable to catabolise the excess VLDL proportionately. Hyper triglyceridemias in Caucasian population is associated strongly with a two allele polymorphism on chromosome 11 near coding sequence for apolipoprotein CIII. Apo CIII is a major constituent of chylomicrons and VLDL. This inhibits LPL and also inhibits uptake of TG rich particles and their remnants.

Elevated Remnant Chylomicron And IDL s

There is increased accumulation of remnant chylomicron remnant and IDLs in patients with type III hyperlipoproteinemia due to a defect in the catabolism. A mean cholesterol elevation to 450mg/dl and triglyceride elevation upto 700mg/dl is observed in these patients there will be a reduced conversion of VLDL to LDL resulting in a low LDL cholesterol

level. There is an increased incidence of premature CAD ,peripheral vascular disease and stroke due to the accelerated atherosclerosis .Normal clearance occurs through the remnant and LDL receptors on the hepatocytes through its recognition by apoE. This impaired in persons with apoE2 allele wherein the defective receptor binding activity is only 1 to 2%.This results in a difficulty in clearing the remnant chylomicrons post prandially , but do not have a fasting hyperlipidemia. The patho gnomonic lesion in typeIII disease is xanthoma striata Palmaris which is characterised by a yellow or orange discoloration of the creases of palms or digits.

Low or undetectable levels of apoE due to homogenous mutation of apo E is described. There is increased atherosclerosis with high plasma VLDL levels and IDL cholesterol levels.

Elevated Lp(a)

Higher levels of Lp(a) is described to be an independent risk factor for coronary artery disease. The range of Lp(a) levels vary from <0.1 to>200mg/dl. Levels greater than 20mg/dl has an increased risk of CAD. Lp(a) levels more than 39mg/dl is observed in many patients with premature CAD. Lp(a)structurally is made of apoB which is bonded to apoA by a bisulfide bond. Patients with smaller apo(a)molecules are at a

higher risk of premature CAD and Lp(a) levels are related inversely to apo(a) size. The gene for Lp(a) is located on chromosome 6 very close to that of plasminogen gene . Lp(a) has both thrombogenic and atherogenic properties due to its interference with fibrinolysis due to its plasminogen like properties. Lp(a) competitively inhibit plasminogen binding for binding with thrombin finally resulting in prevention of assembly of fibrinolytic mechanisms. Elevted Lp(a) is seen both in patients and their relatives with premature myocardial infarction, thus screening of their relatives is important.

CHOLESTEROL RATIOS AND OTHER BIOMARKERS PREDICTING CARDIOVASCULAR DISEASE RISK

CVD risk assessment based solely TC or LDL-C may be suboptimal., many new lipoprotein ratios “and atherogenic”indices are there which improve CVD risk assessment . Risk quantification for CVD better than LDL-C or TC. In order to incorporate HDL-C for the risk assessment of CVD ratio of TC/HDL-C and non–HDL-Ci s used. The TC:HDL-C ratio,is known as the atherogenic index or Castelli index. Commonly used ratio is LDL-C/HDL-C ratio. These ratios gives us an easy assessment of atherogenic risk because an increased TC concentration especially LDL-C, is an indicator of increased atherogenic

lipoproteins, also an increased HDL-C is an indicator of an increased atheroprotective lipoproteins. The TC/HDL-C ratio was superior for discriminating CHD risk compared to LDL-C level. In individuals with normal or near normal LDL-C but has an increased CVD risk profile, due to diabetes, pre diabetes, or metabolic syndrome there is an increased risk with increased TC/HDL-C.

Two thirds of plasma cholesterol is contained in LDL-C. The LDL-C/HDL-C ,TC/HDL-C ratio are similar due to this reason. Patients who have high triglyceride (TG) levels, this ratio provides a better CVD risk assessment than LDL-C alone. Increased risk for CHD was seen in individuals with an LDL-C/HDL-C ratio of greater than 5 and TG concentrations of greater than 204 mg/dL than individuals with lower value .Patients having very high TG concentrations, estimation of LDL-C with the Friedewald equation was not reliable, in whom TC/HDL-C ratio is a more better marker of atherosclerotic risk, so is non–HDL-C.

Subtracting HDL-C from TC gives the Non–HDL-C value , it includes LDL, VLDL, IDL, and lipoprotein(a) Non HDL c measures the cholesterol content of all lipoprotein particles that are atherogenic. It is a better CVD risk marker than LDL-C and also the single best lipid parameter which predicts the future risk of CAD.

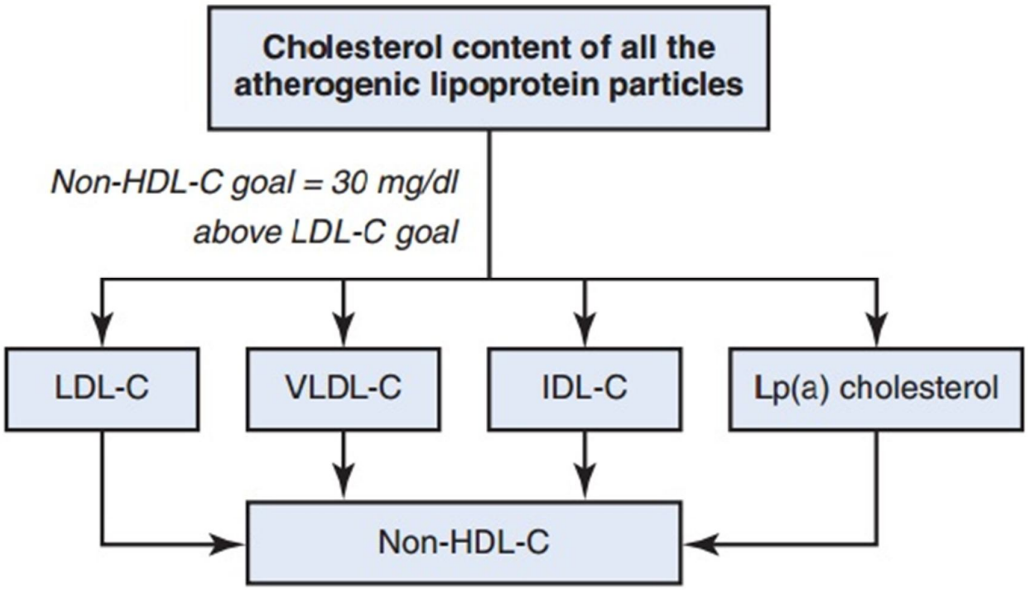


Figure 3 Non HDL cholesterol

Non–HDL-C is also a stronger marker predicting future CVD risk in patients on statins.

There is a strong association between apoB levels and fatal MI. Increase in apoB and decrease in apoA-I concentrations were associated with a higher risk for fatal MI.

Oxidized LDL

Oxidized LDL (ox-LDL) is a lipid peroxidation product from oxygen free radicals . Oxidation of polyunsaturated fatty acids by oxygen free radicals produces a reactive species causing a modification of both lipid and protein components of LDL .This causes apo B-100

degradation to peptide fragments that are which undergo further modification into oxidized fatty acids. Accumulation of oxidized LDL and its by products on the wall of the arteries, causes activation of the inflammatory response and t recruitment of T cells and monocytes. Monocytes are converted into macrophages following oxidized LDL uptake, subsequently forming foam cells causing initiation of cholesterol as a fatty streak. Ox LDL has atherogenic properties is useful in the diagnosis, management, and prediction of stable and acute CAD. Oxidized LDL is also a predictor of CAD events in the future. In males who donot have a history of CAD or diabetes but having adjusted traditional risk factors, oxLDL was the predicts future CAD events strongly compared to lipid profile and traditional risk factors. Ox-LDL acts as an independent predictor of the severity and prevalence of subclinical atherosclerosis which was identified by ultrasound evaluation of the femoral and carotid arteries .There is a positive correlation between ox-LDL and CRP, IL-6, and TNF- alpha levels .

Evaluation of plaque with immunohistochemical staining showed an elevated oxLDL in foam cells derived from macrophage in patients with acute myocardial infarction. Only a few areas were stained for ox-LDL macrophages in the samples of patients from stable angina pectoris . This shows that acute coronary syndrome severity is predicted by ox-

LDL. Levels of serum soluble lectin-like ox-LDL receptor can be used as predictor of ACS onset atherosclerotic plaque rupture as serum lectin-like ox-LDL receptor is significantly elevated in ACS patients. Circulating oxidized LDL level measurement is not available widely normal and at risk values have not been established definitively so further studies are needed for the same .

Small Dense LDL

The size, type, number of LDL particle is not taken into account in a standard lipid panel lab measurement which measures the LDL mass in a unit of serum.LDL particles are of different sizes from small, medium and large the risk related to LDL varies on the concentration of LDL particle sizes . The initial step small dense LDL production occurs in liver when excess triglycerides attached to VLDL are exchanged by CETP for cholesterol ester leading to the production of triglyceride rich LDL which undergoes lipolysis by hepatic lipase to produce smaller and denser LDL particles(<255A) .

The small, dense LDL particles are thought to have comparatively long periods of time in the systemic circulation since they bind less avidly to the LDL receptor. Small, dense .LDL has potentially more atherogenic properties than larger LDL particles due to more circulation time, and

more oxidative modification. Patients with higher small, dense LDL levels have an increased clinically manifest CAD, independent of other cardiovascular risk factors. and LDL levels. Recent studies showed an increased levels of small, dense LDL in patients with the metabolic syndrome . There are many limitations to the routine LDL particle size assessment even though there are several commercially available sources The ability of small, dense LDL in predicting cardiovascular events independently is significantly decreased when LDLs are brought down to current treatment targets and low non-HDL cholesterol, body weight, and smoking, are managed effectively. The predictive value of LDL particle size may not be additive to non HDL cholesterol and triglyceride incorporated models. So its value to current lipid measures is not clear. The fact that small, dense LDL clearly predicts CAD events is proven , but clarity regarding altering LDL size leading to decreased CAD events independent of any effect on lowering LDL is not established .As, patients with increased levels of small, dense LDL can be predicted on the the basis of presence of the metabolic syndrome, measuring small dense LDL becomes questionable.

Therapeutic options to change LDL particle size like statins, niacin, and fibrates are not evaluated in clinical trials with regard to LDL particle size. Measurement of lipid parameters, beyond a standard fasting

lipid profile is not recommended for cardiovascular risk assessment in asymptomatic adults.

Remnant Cholesterol

Remnant cholesterol is the cholesterol content of the triglyceride-rich lipoproteins subset called remnants which includes remnant chylomicron, VLDL, and IDL during non fasting state, and VLDL and IDL during fasting . Hydrolysis of triglyceride by lipoprotein lipase occur rapidly in most persons leading to the production of chylomicron remnant from chylomicron . Levels of remnant cholesterol correlates highly with triglyceride. There is an exchange of triglycerides and cholesterol between HDL and remnants, and there is an inverse correlation between the levels of HDL cholesterol and remnant cholesterol. It is difficult to determine whether the low HDL levels or the high remnant cholesterol and triglycerides levels is the cause of the increased risk of CAD . Non fasting elevated levels of triglycerides are more a more accurate predictor of cardiovascular disease risk of than that of fasting levels of triglycerides. Fasting is defined as not eating for at least 8 hrs and most of the people are in the non fasting state. So the level of remnant cholesterol in non fasting state with and its association with cardiovascular disease is important. Non fasting remnant cholesterol to

HDL ratio was also associated significantly with increased IHD risk. Remnant cholesterol levels are genetically determined partly determined by various factors like as diet, obesity, alcohol intake, and physical activity . Many genetic variants influences the levels of remnant cholesterol levels like mutations in the LPL, APOC2, APOA5, LMF1,andGPIHBP1genes . TRIB1(rs2954029),GCKR (rs1260326), and three variants inAPOA5(rs651821, rs3135506, and rs619054) have higher non fasting triglycerides, remnant cholesterol, and LDL levels , and a lower HDL.TRIB1andAPOA5 have association with increased CAD risk but, GCKR variant had no association with IHD risk .TRIB1encodes tribble-1 protein with mitogen-activated protein kinase regulatory effect .During lipoprotein metabolism , the CETP exchanges triglycerides between. remnants and HDL particles for cholesterol esters, leading to inverse correlation between remnant l and HDL cholesterol levels .Almost all of the genetic variants with elevated remnant cholesterol levels are associated with low HDL levels and also elevated LDL levels. This has previously made it difficult to separately determine the causality of elevated levels of remnant cholesterol and low levels of HDL cholesterol on risk of IHD.

Remnant lipoprotein compositions are different in terms of lipids and apolipoproteins because of three main reasons :-remnants are at different stages lipolysis of triglyceride ,there is an apolipoproteins and lipids exchange with other lipoproteins, remnants synthesis is by two different pathways, i.e. the endogenous and the exogenous pathways.

This causes a practical difficulty in creating an assay which is capable of measuring all remnants at a same time. So non fasting remnant cholesterol is calculated as non fasting TC minus HDL minus LDL. The advantage of this calculation is that it is inexpensive, as it can be done from a lipid profile result, in the non fasting. The disadvantage is that the precision of this method is low.

The mechanism by which remnant cholesterol causes ischemic heart disease is simple and straight forward. Remnant cholesterol enters into the intima of the arterial wall which leads intimal cholesterol accumulation leading to atherosclerosis atherosclerosis and finally to IHD.

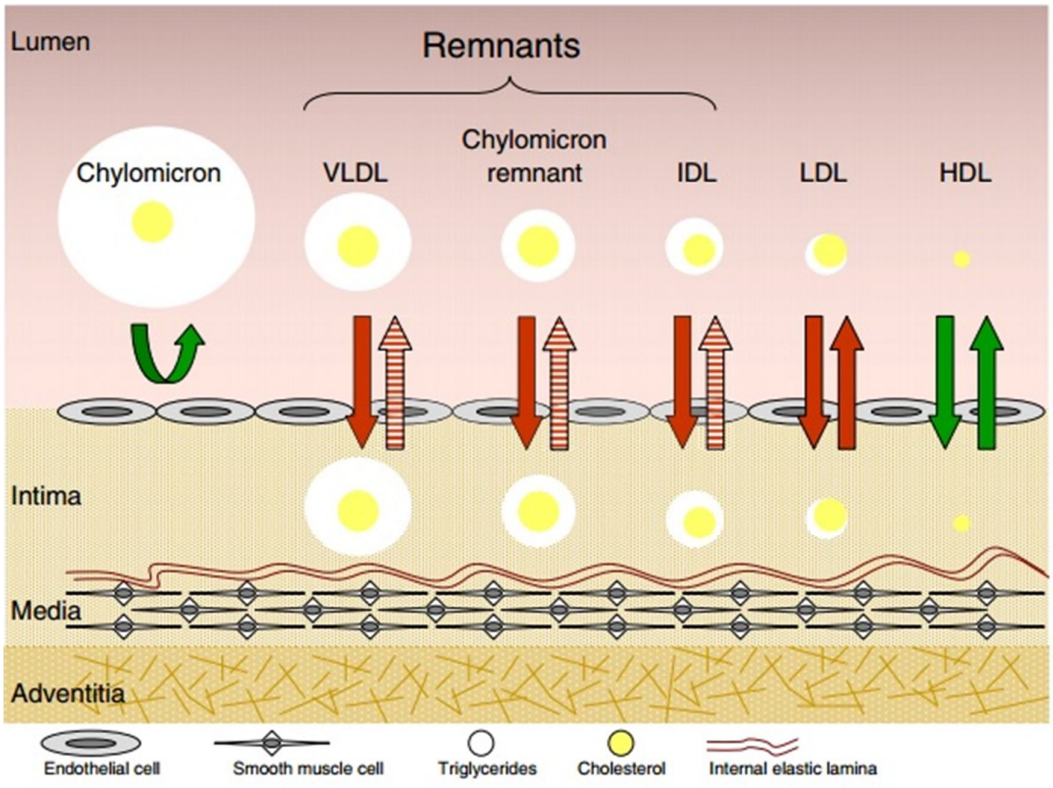


Figure 4 Mechanism of remnant and LDL trapping and atherosclerosis

The ability of the lipoprotein to enter the arterial wall and get trapped is based on their size. Large VLDL particles and chylomicrons are too big to enter the wall of arteries. Remnants can penetrate the intima of arteries and get trapped in arterial wall connective tissue and accumulate eventually there. Patients with homozygous LPL gene mutation , which causes chylomicronemia and elevated large chylomicrons and VLDL levels , have no increased risk of CAD but an increased risk of pancreatitis. Remnants, have the ability to bypass the

oxidation process before macrophages uptake causing foam cell formation and atherosclerosis.

Remnants also act by pathways other than cholesterol accumulation in the arterial wall for atherosclerosis and IHD. Remnants are associated with mechanisms causing endothelial dysfunction, like defective vasodilatation and increased inflammation and also in disruption of plaque and formation of thrombus . Elevated remnant cholesterol levels had a causal association with low-grade inflammation and CAD ; whereas elevated LDLs had association with CAD only not with inflammation .Similar results were seen in persons without obesity and diabetes mellitus. This shows that atherosclerosis caused by increased LDL levels and lacks an inflammatory component, and elevated remnant cholesterol levels is the driving force of the inflammatory component of atherosclerosis. Obesity is the commonest cause of high remnant cholesterol and triglycerides and diabetes mellitus which is poorly controlled and alcohol intake in an excess amount are also common causes of high remnant cholesterol levels. Elevated estrogen levels in women , during pregnancy or from oral contraceptives or hormone replacement therapy, increased triglyceride levels , and remnant cholesterol levels. Chronic renal and hepatic disease, drugs, like oral glucocorticoids, leads to remnant cholesterol level elevation. Beyond

these factors genetic factors also have a role in determining the extent of triglycerides and remnant cholesterol level elevation .For example patients with chylomicronemia syndrome with N25 mmol/L (N2200 mg/dL) triglycerides have an increased risk of pancreatitis compare to CAD. When the triglyceride levels are lowered in these patients, there is an increased risk of CAD and had increased risk factors for CAD. This paradox is explained by increased ability of lipoprotein to penetrate and get trapped when triglyceride levels are lowered when compared to , large size of lipoproteins having difficulty to enter into the intima of arteries to cause atherosclerosis.

The strategies to decrease remnant cholesterol include lifestyle changes and pharmacotherapy. The most effective lifestyle modifications that lower remnant cholesterol levels are weight reduction ,cessation of alcohol intake, decreasing dietary saturated fat intake , cessation of smoking, and finally increasing physical activity .There is a increased clearance of VLDL in the liver and decreased hepatic secretion due to lifestyle changes causing a reduction in level of remnant cholesterol.

Therapeutic agents causing decrease in remnant cholesterol levels are statins, fibrates and niacin. RCTs results with statin showed benefit in lowering triglycerides and non-HDL cholesterol (LDL cholesterol plus

remnant cholesterol)..RCT s with niacin in added to statin or fibrate yielded results that are conflicting regarding cardiovascular disease risk reduction.

First choice of treatment in patients with hyperlipidemia is statins ; fibrates or niacin is added in patients with hypertriglyceridemia, and high remnant cholesterol levels, after taking statin treatment and lifestyle modification. Other option to lower remnant cholesterol levels is omega-3 fatty acids, or fish oil, which was used to lower triglycerides to decrease the risk of pancreatitis in patients with hypertriglyceridemia. Recent trial data showed a reduction in remnant cholesterol level using omega 3 fatty acids. Many newer agents are also tested including drugs that target apolipoprotein production . Ipomersen which is an ApoB antisense oligonuclotide was approved for use in homozygous familial hypercholesterolemia . Lomitapide is an MTP inhibitor approved in patients of homozygous familial hypercholesterolemia . These drugs caused increased lipid content in liver. Next newer drugs developed are antibodies against PCSK9 plasma proprotein convertase subtilisin/kexin type 9 The normal action of PCSK9is to binds to the LDL receptor and its degradation, so PCSK9 inhibition causes an increases in the number of LDL receptors. This in turn causes uptake of LDL and remnants from plasma.

ANATOMY OF CORONARY CIRCULATION

The left main coronary arteries arise from the left coronary sinus and and right coronary artery from right coronary sinus. Coronary sinuses are situated distal to the aortic valve at the aortic root. Left main coronary artery divides into left anterior descending (LAD) and left circumflex artery (LCX) approximately after 2.5 cms from its origin, the former runs in the inter ventricular groove and the later through the atrio-ventricular groove. The anterior two thirds of the inter ventricular septum, anterior , apical, and lateral walls of the left ventricle is supplied by the LAD. The inferior and posterior segments of the left ventricle is supplied by the LCX s. The course of right coronary artery (RCA) is along the right atrio ventricular groove and its acute marginal branch supplies right atrium, right ventricle and the infero posterior wall of LV. The posterior descending branch can arise from right coronary or from left circumflex artery. Depending on the origin of posterior descending branch patients are classified to have a dominant right system or left system. 85% of the people will have a dominant right system. Right coronary artery supplies SA node in 60% of the patients and 40 % by left circumflex artery. AV nodal supply is predominantly by the RCA. This causes sinus bradycardia and AV nodal block in RCA occlusion.

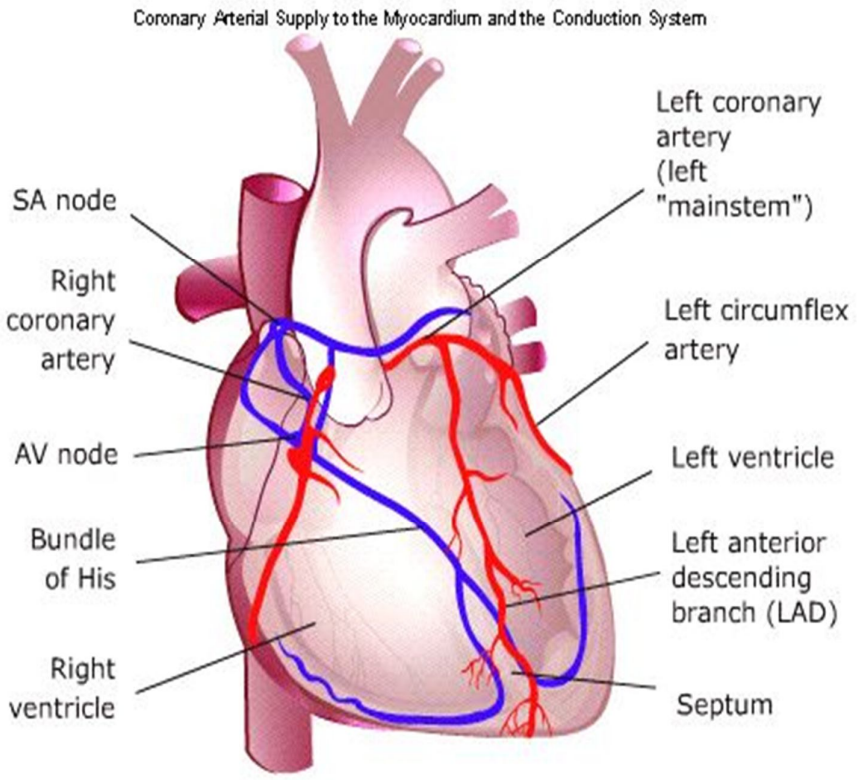


Figure 5 Coronary Circulation

STEMI PATHOPHYSIOLOGY

Atherosclerotic occlusion of the coronaries is the predominant cause of STEMI. The plaque with a rich lipid core and a thin fibrous cap are more susceptible for plaque rupture acutely .Following rupture the contents of the plaque is exposed to the blood , favouring thrombogenesis .Release of collagen, ADP, epinephrine, serotonin causes platelet adhesion and aggregation . The exposure of tissue factor in exposed endothelial cells triggers the coagulation cascade.

Fibrin is produced and causes cross linking of platelets by fibrin strands leading to a mural thrombi formation at the plaque disruption site of causing culprit coronary artery occlusion..

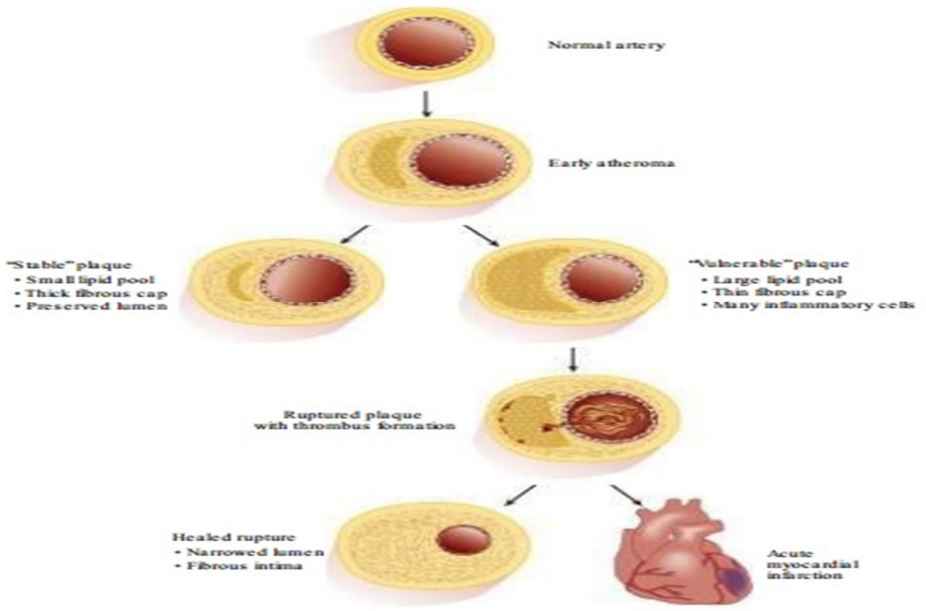


Figure 6 Atherosclerotic plaque and its fate

CLINICAL PRESENTATION

Diagnosis of MI relies on the clinical history and physical examination and direct the diagnostic evaluation. Although pressure or tightness is a typical presentation of myocardial ischemic pain, some patients with ischemic chest symptoms deny any “pain,” but rather complain of shortness of breath or a vague sense of anxiety Myocardial ischemic discomfort is typically sub sternal in location with radiation to the neck, jaw, shoulder, or arms . Pain occurring solely above the

mandible or below the epigastrium is rarely angina..Symptoms develop over minutes, and exacerbated by activity and relieved by rest. Diaphoresis, dyspnea, nausea, fatigue, faintness, and belching can also be present with chest pain caused by myocardial ischemia. These symptoms may exist alone as ischemia equivalents Dyspnea can accompany myocardial ischemia and indicates a higher risk for fatal complications. Nausea and vomiting can occur in an MI (commonly in inferior wall MI), and related to vagal reflexes or ventricular receptors stimulation as part of the Bezold-Jarisch reflex. Less common presentations include sudden loss of consciousness, acute confusional state, unexplained hypotension, arrhythmia, a sensation of profound weakness. They may be with or without chest pain. Painless myocardial infarction is usually seen in diabetics.

PHYSICAL FINDINGS

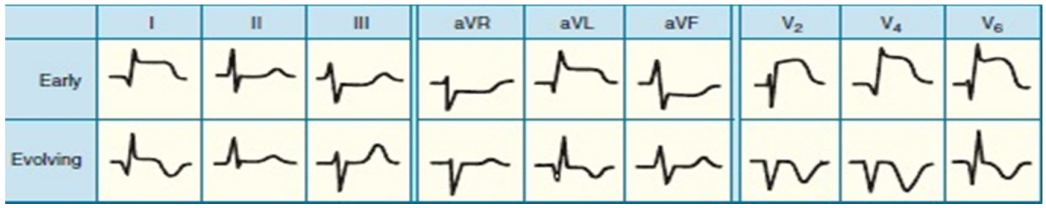
Patients will be anxious, uncomfortable, or diaphoretic cyanosis or pallor may be evident in patients with early complication of MI. Tachycardia and hypotension indicates an emerging cardiogenic shock because of dysfunction of left ventricule or mechanical complications The JVP is often normal in acute MI. Chest palpation may reveal a dyskinetic ventricle in patients with large infarctions or previous MI.

Auscultation reveal S3 or S4, due to systolic or diastolic dysfunction. Mitral regurgitation or ventricular septal defect causing a harsh murmur indicates a mechanical complications of MI. Pericardial friction rubs indicates pericardial inflammation occurring in late presentations of MI.

DIAGNOSIS

The diagnosis of STEMI is established by ECG, cardiac biomarkers and cardiac imaging.

Electrocardiography - ST elevation at the J point in two contiguous leads with greater than 0.1 mV in all leads except V2to V3.In V2toV3 greater than 0.2 mV in men aged more than40 years, and greater than 0.25 mV in men less than40 years, or greater than 0.15mV in women.



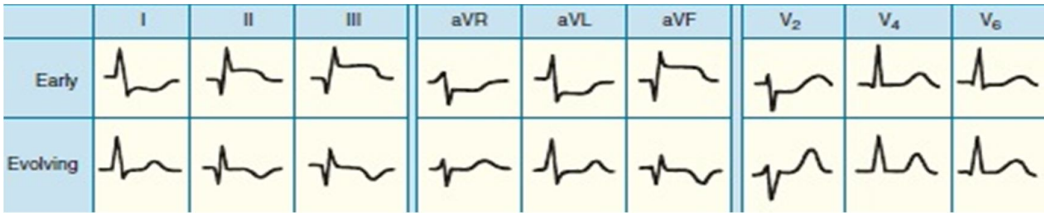


Figure 7 STEMI Ecg

Cardiac Biomarkers

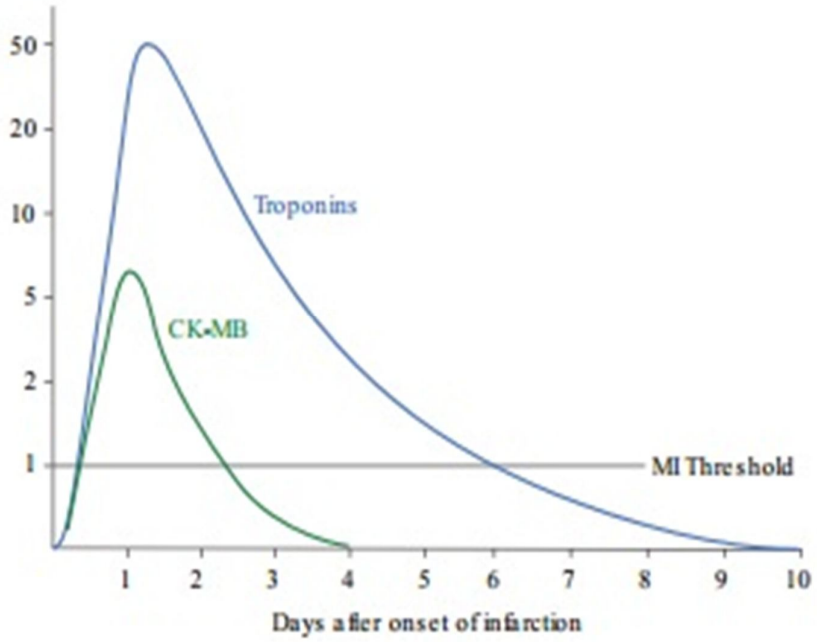


Figure 8 Cardiac biomarkers

Proteins released into the circulation from the necrotic heart muscle after STEMI are called as cardiac biomarkers . Most used biochemical markers for MI diagnosis are the cardiac Troponin T & I.

Normally troponins are not detectable in the blood but levels increase twenty times in myocardial infarction. They remain for 7 to 10 days after STEMI. Next biomarker is the creatinine phosphokinase but does not lack specificity for STEMI as levels may be high in skeletal muscle disease ,trauma, im injections. MB Isoenzyme is less seen in extracardiac tissue has higher specificity for STEMI .

CARDIAC IMAGING

When the ECG is non diagnostic presence of wall motion abnormality in 2D echocardiography is a very useful test but cannot distinguish old myocardial scar from acute ischemia. ECHO also assesses the left ventricular function which in turn predicts the future prognosis. ECHO is used to identify other of STEMI complications like LV thrombus , ventricular aneurysm, pericardial effusion ,mitral regurgitation and ventricular septal defect. Myocardial perfusion imaging, radionuclide ventriculography are lack sensitivity & specificity and not done routinely in clinical practice . Cardiac MRI with gadolinium also helps in detecting MI .

MANAGEMENT

ASPIRIN – 160 to 325 mg tablet is given stat and is asked to be chewed and swallowed(

2)OXYGEN in patients with hypoxemia via nasal prongs or facemask at 2 – 4 L / min for 6 to 12 hrs .

3)SUBLINGUAL NITROGLYCERIN –Three doses can be given at about 5 min intervals. It decreases the chest pain and also myocardial oxygen demand by preload reduction and dilates the blocked coronary

arteries thereby increasing the myocardial oxygen supply. Nitrates are contraindicated in hypotension (systolic BP < 90), right ventricular infarction and inferior wall MI with hypotension.

4)MORPHINE – used to relieve the chest pain also reduces arteriolar and venous vasoconstriction which is sympathetically mediated.

4)IV BETA BLOCKERS –used to relieve pain in MI. Avoided in patients with heart failure, hypotension asthma, heartblock etc..

Glucocorticoids and NSAIDS (except Aspirin) are not used as they impair the healing of the infarct and may increases chance of myocardial rupture.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

PCI done in patients without preceding fibrinolysis is called as primary PCI. Most effective in opening up of blocked coronaries . Treatment of choice in cardiogenic shock, doubtful diagnosis, increased bleeding risk

FIBRINOLYSIS – Fibrinolytic agents are streptokinase, tenecteplase(TNK), reteplase(rPA). These act by conversion of plasminogen to plasmin which lyses the fibrin in the thrombi. The benefit of fibrinolysis is seen 12 hours from the start of infarction. Absolute contraindications

are prior hemorrhagic CVA, ischemic stroke within the past 1 year, BP> 180 /110, active internal bleeding, suspicion of aortic dissection and advanced age. Failed reperfusion by fibrinolytic therapy causing persistent chest pain and ST segment elevation more than 90 minutes, then angiography and stenting should be done and is called as rescue PCI.

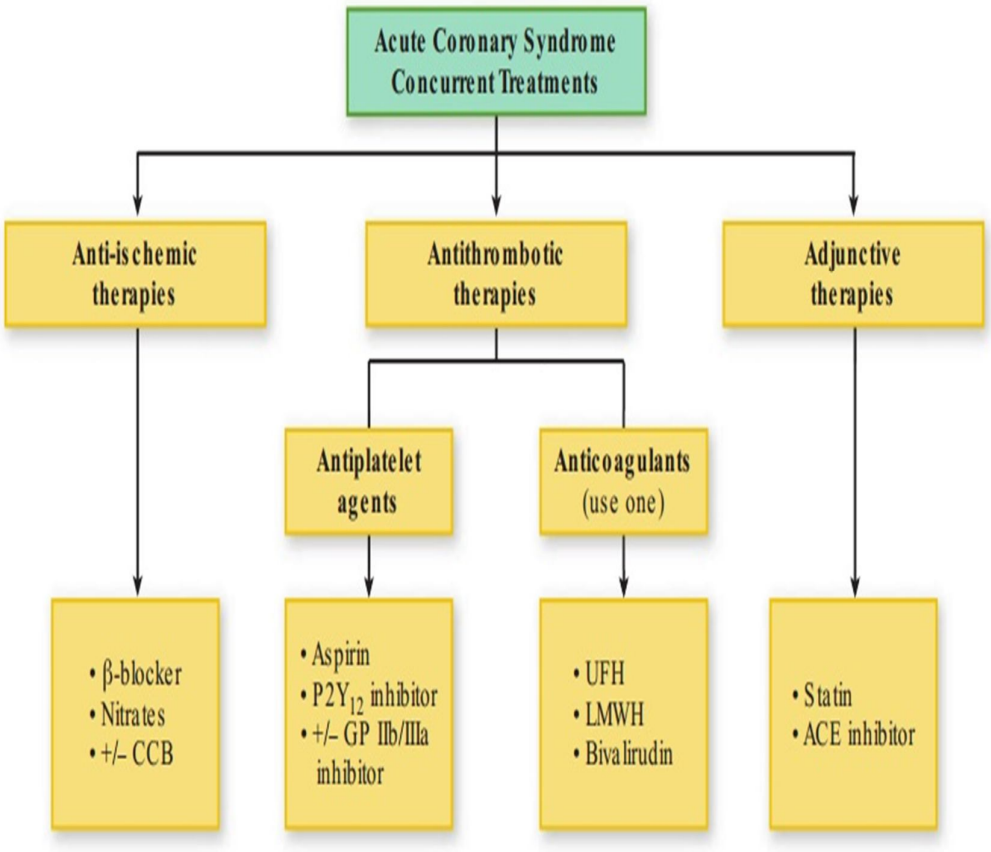


Figure 9 Concurrent treatments in ACS

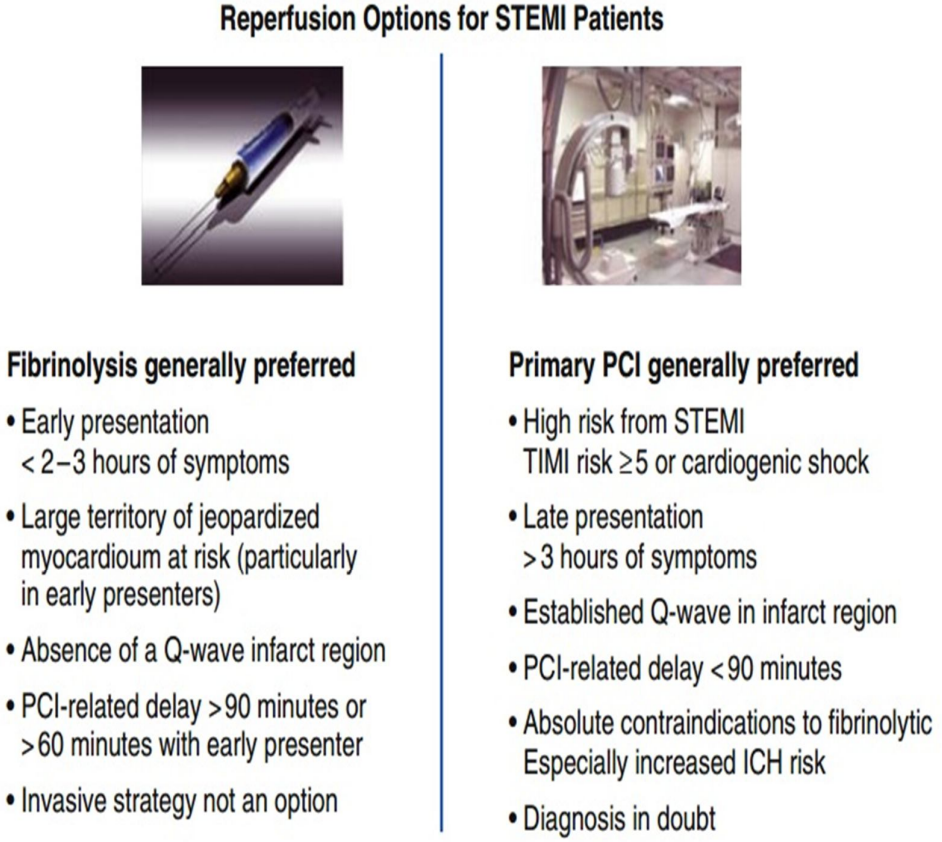


Figure 10 Fibrinolysis v/s Primary PCI

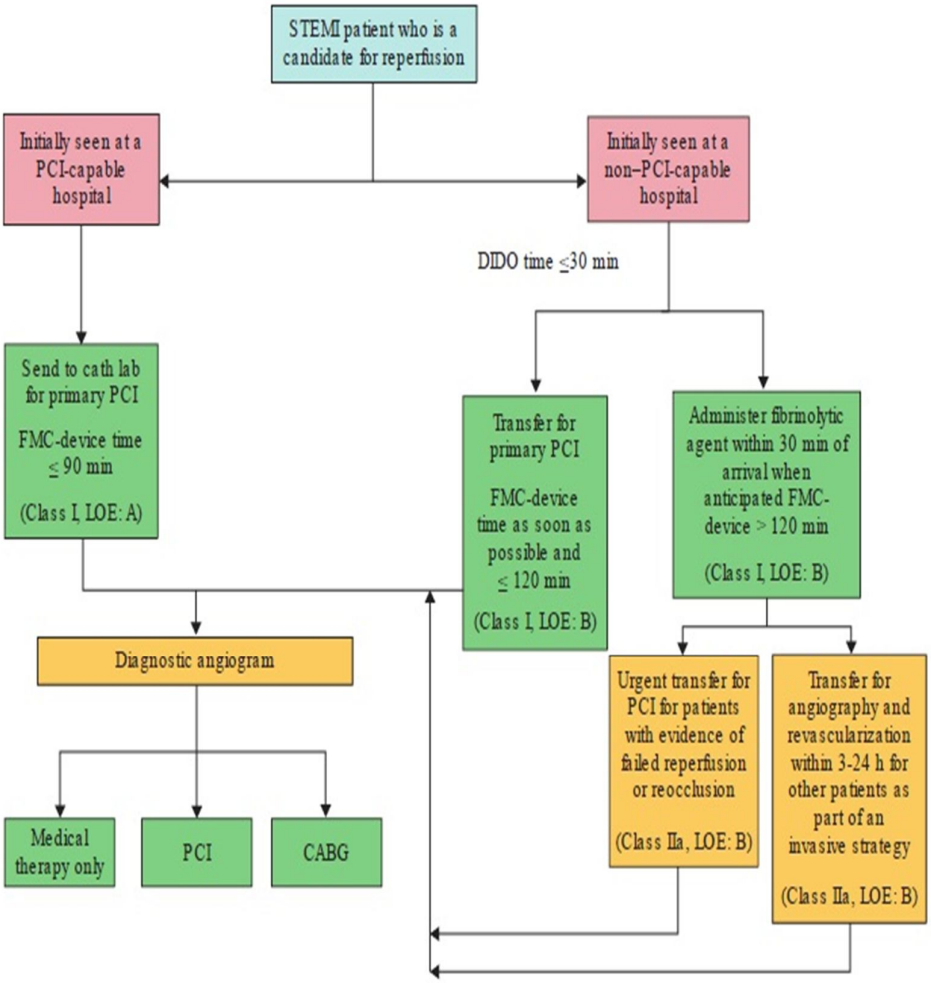


Figure 11 Management algorithm in STEMI

MATERIALS AND METHODS

SOURCE OF STUDY:

Data consists of primary data collected by the principal investigator directly from the patients who are admitted in the ICCU of Government Coimbatore Medical College and Hospital for STEMI as cases and age and sex matched healthy individuals attending the general medicine opd as contol.

DESIGN OF STUDY: Case control study

PERIOD OF STUDY: One year, July2016- June2017.

SAMPLE SIZE: 100

- 50 patients with STEMI of age group less than 40 years
- 50 patients without STEMI of age group less than 40 years

INCLUSION CRITERIA:

- Patients diagnosed to have STEMI based on ECG.
- Age less than 40 years.

EXCLUSION CRITERIA

- ❖ Patients with prior history of dyslipidemia on statins.
- ❖ Patients with prior history of myocardial infarction.
- ❖ Patients with renal insufficiency ,liver disease.
- ❖ Patients not capable of giving consent (psychiatric patients).
- ❖ Patients not willing to participate in the study (who refused to consent)
- ❖ Pregnant and lactating women.

METHODOLOGY

The study is will be undertaken on the patients admitted in ICCU of Coimbatore Medical College and Hospital, Coimbatore during the study period July 2016 to June2017). A total of 100 patients out of which 50 patients aged less than 40 fulfilling the criteria for ST elevation myocardial infarction and 50 age and sex matched patients without myocardial infarction or cardiovascular disease are included in the study based on the inclusion/exclusion criteria.

The list of the patients enrolled in the study is appended along with the dissertation. The study excludes minors, pregnant women, mentally-ill and non-volunteering patients.

The study is proposed to be conducted after obtaining informed signed consent from the patients. The principal investigator, after obtaining informed signed consent from the patients to participate in the study conventional cardiovascular risk factors like family history of myocardial infarction, smoking ,alcohol intake, diabetes mellitus and systemic hypertension were recorded . Venous samples were drawn at the day of study enrolment in control patients or up to 48 hours after myocardial infarction in cases after an overnight fast or irrespective of the fasting status . Samples were analyzed according to the hospital laboratory's standard procedure. Total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides were estimated .Non fasting remnant cholesterol was calculated as total cholesterol minus HDL cholesterol minus LDL cholesterol. Discrete data were presented as counts and percentages, continuous data as means and standard deviations . The unpaired t test and the chi square test were used for comparison between groups, as appropriate analysed using SPSS Software.

- **INVESTIGATIONS :**

- 12 lead ECG
- Total cholesterol
- Triglycerides
- HDL cholesterol
- LDL cholesterol

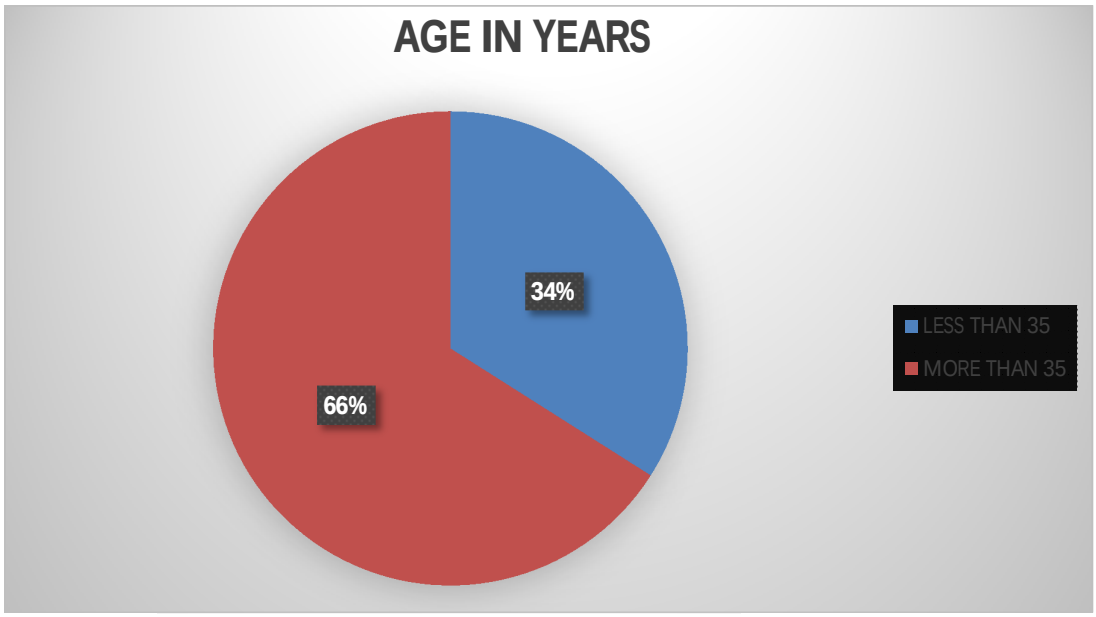
OBSERVATIONS AND RESULTS

Table 3 Age Distribution

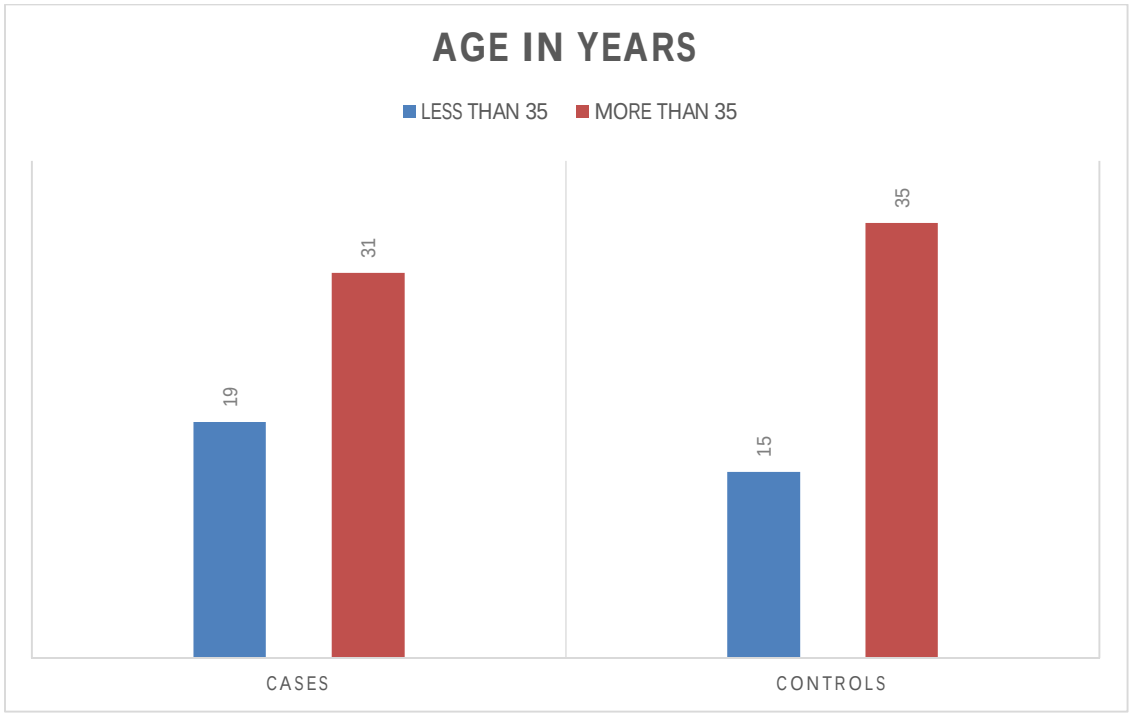
AGE IN YEARS	NO OF PATIENTS	PERCENTAGE
LESS THAN 35	34	34%
MORE THAN 35	66	66%

Table 4 Age Distribution Cases And Controls

	PATIENTS	
AGE IN YEARS	CASES	CONTROLS
LESS THAN 35	19	15
MORE THAN 35	31	35
P VALUE - 0.398		
ODDS RATIO - 1.43		
NON SIGNIFICANT		
CHI SQUARE TEST		



Graph 1 Age Distribution



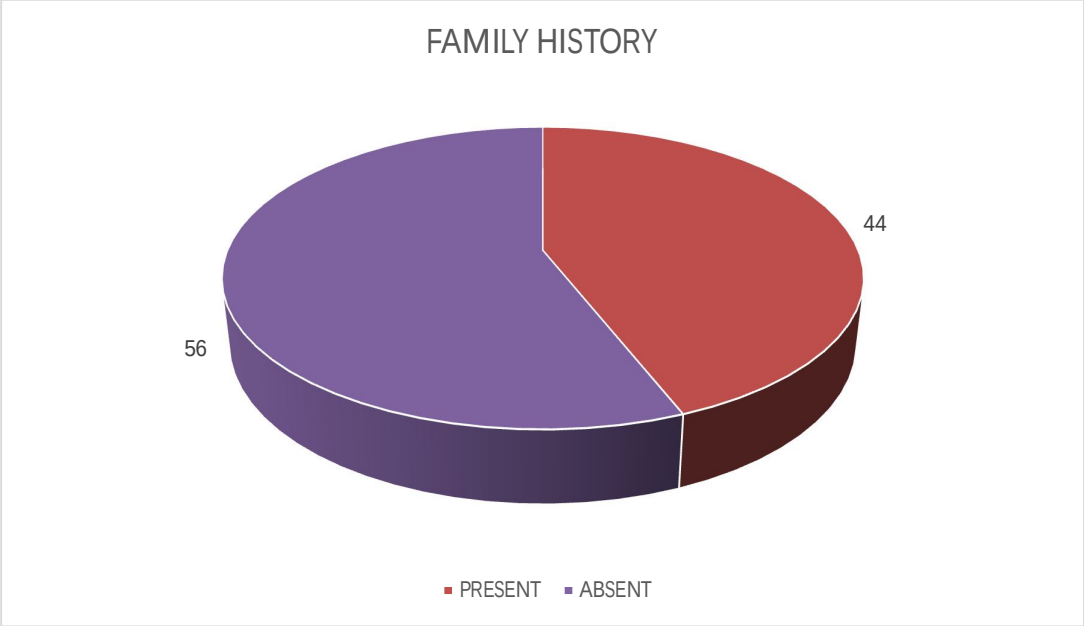
Graph 2 Age Distribution Cases And Controls

Table 5 Family History

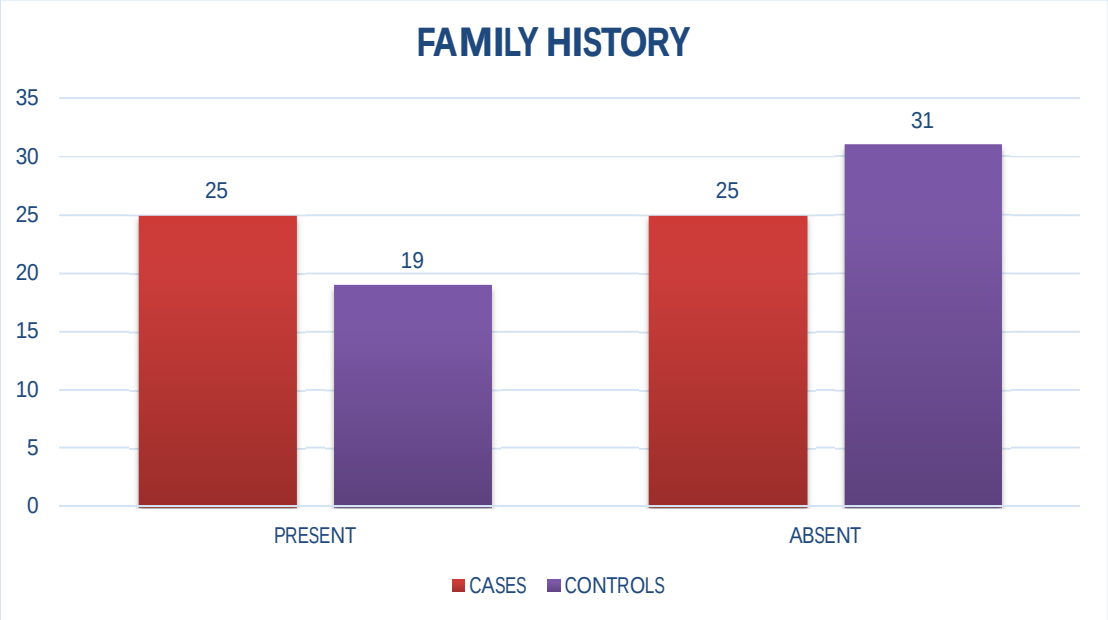
FAMILY HISTORY	NO OF PATIENTS	PERCENTAGE
PRESENT	44	44%
ABSENT	56	56%

Table 6 Family History In Cases And Controls

FAMILY HISTORY	PATIENTS	
	CASES	CONTROLS
PRESENT	25	19
ABSENT	25	31
P VALUE - 0.227		
ODDS RATIO - 1.63		
NON SIGNIFICANT		
CHI SQUARE TEST		



Graph 3 Family History



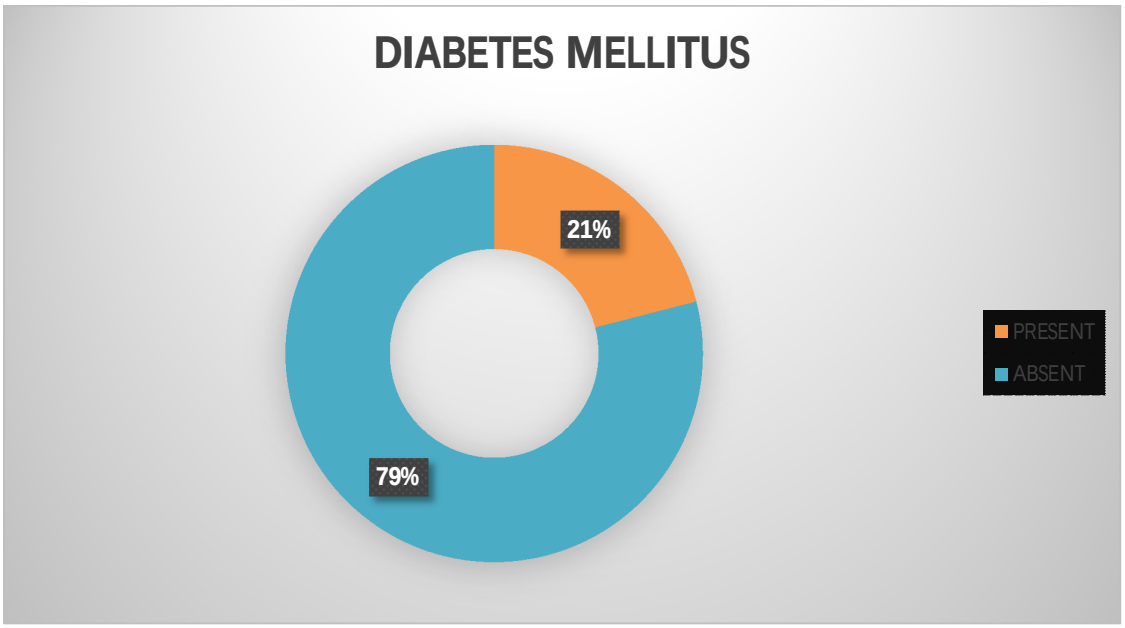
Graph 4 Family History In Cases And Controls

Table 7 Diabetes Mellitus

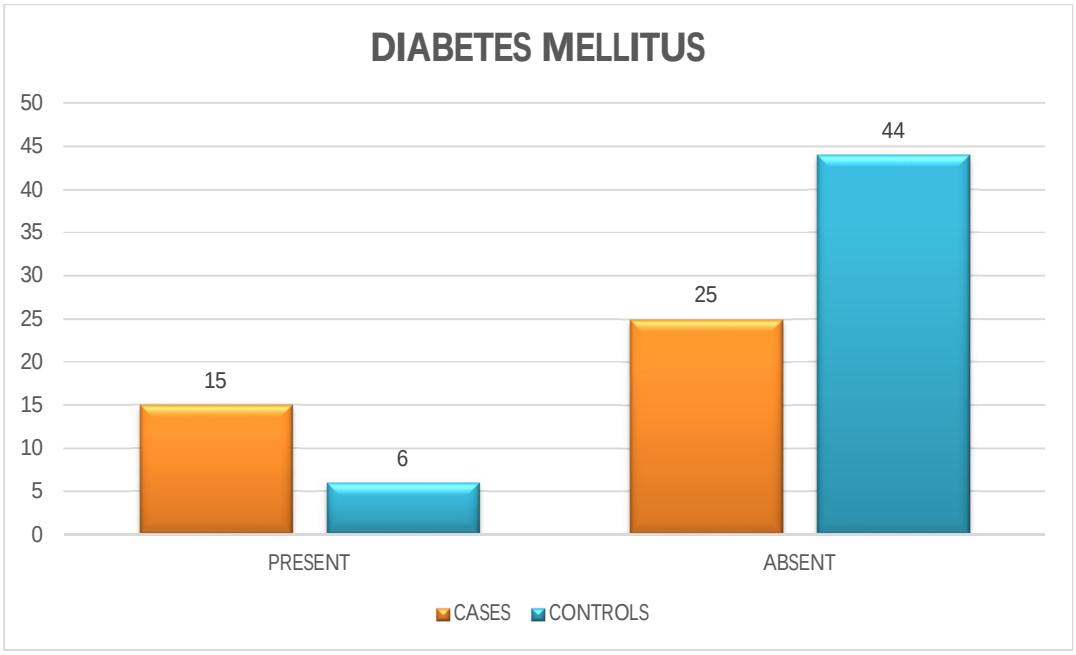
DIABETES MELLITUS	NO OF PATIENTS	PERCENTAGE
PRESENT	21	21%
ABSENT	79	79%

Table 8 Diabetes Mellitus in Cases and Controls

DIABETES MELLITUS	PATIENTS	
	CASES	CONTROLS
PRESENT	15	6
ABSENT	25	44
P VALUE - 0.027		
ODDS RATIO - 3.14		
SIGNIFICANT		
CHI SQUARE TEST		



Graph 5 Diabetes Mellitus



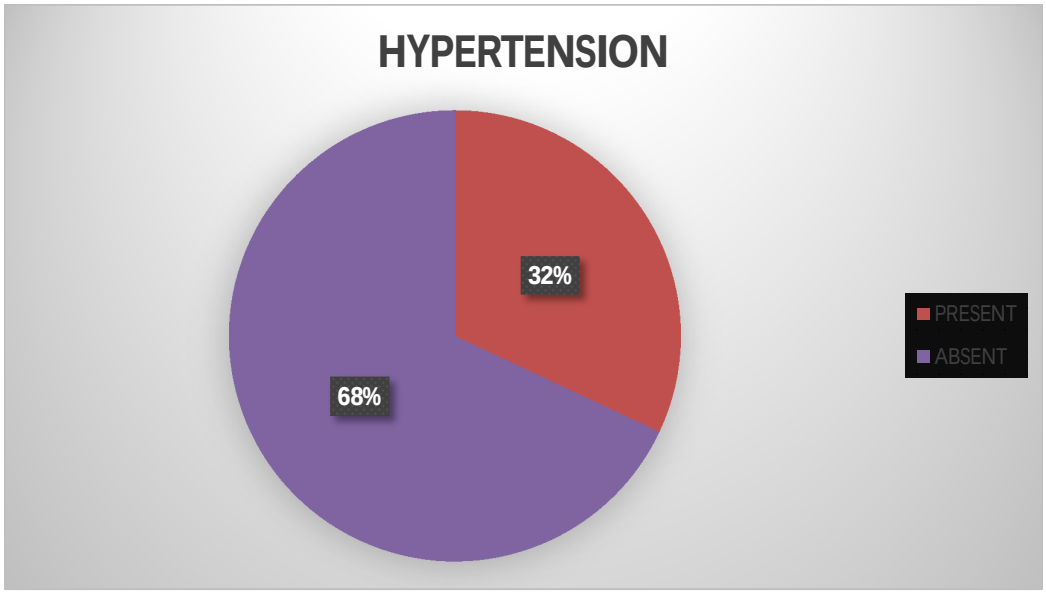
Graph 6 Diabetes Mellitus in Cases and Controls

Table 9 Hypertension

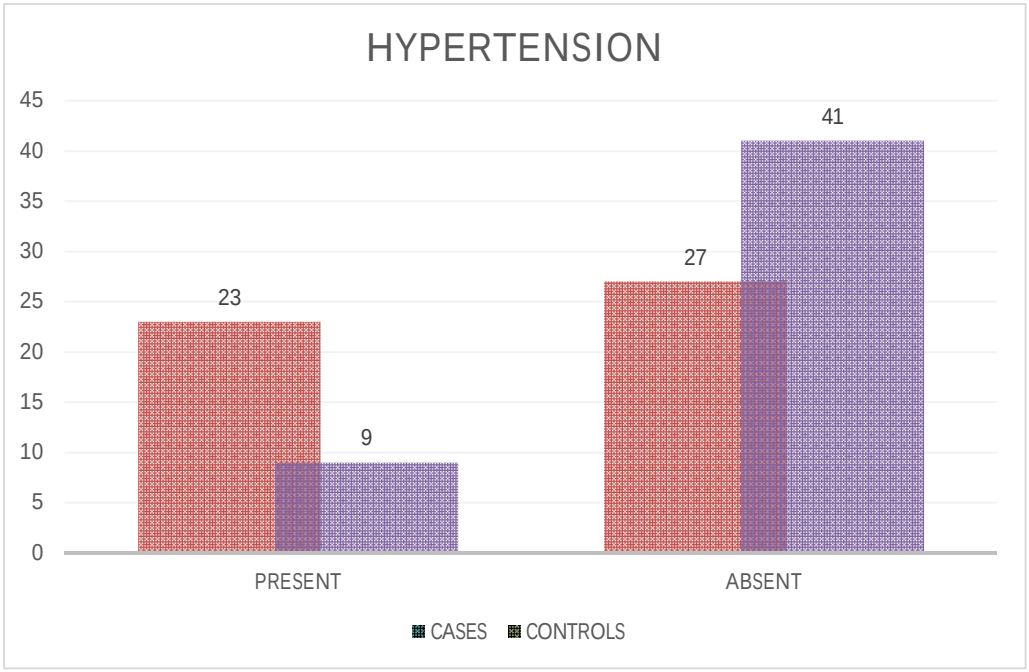
HYPERTENSION	NO OF PATIENTS	PERCENTAGE
PRESENT	32	32%
ABSENT	68	68%

Table 10 Hypertension in Cases and Controls

HYPERTENSION	PATIENTS	
	CASES	CONTROLS
PRESENT	23	9
ABSENT	27	41
P VALUE - 0.003		
ODDS RATIO - 3.88		
SIGNIFICANT		
CHI SQUARE TEST		



Graph 7 Hypertension



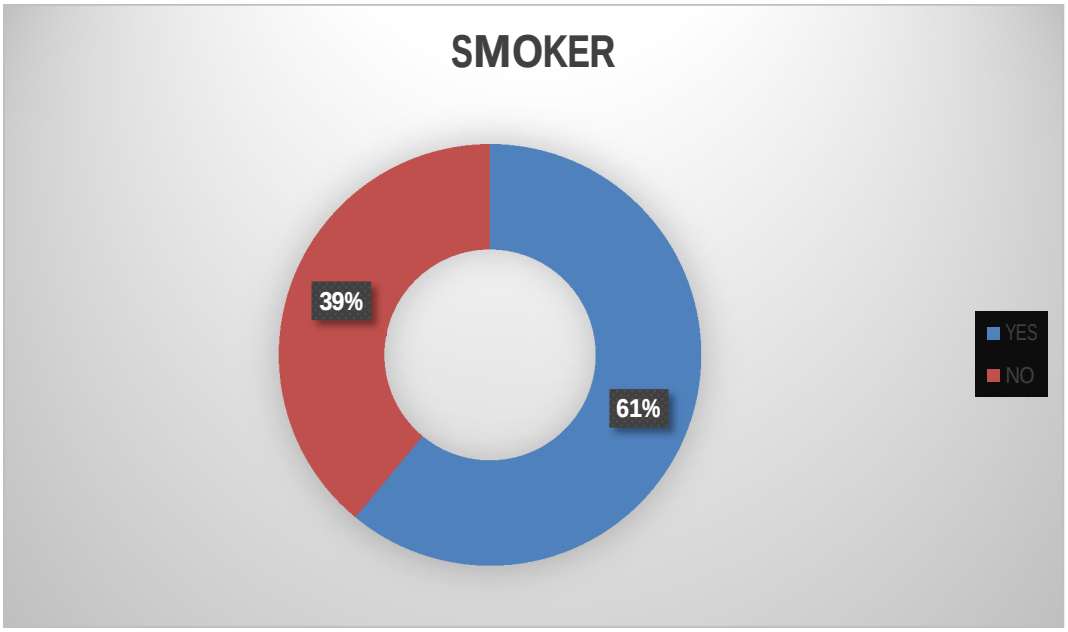
Graph 8 Hypertension in Cases and Controls

Table 11 Smoking

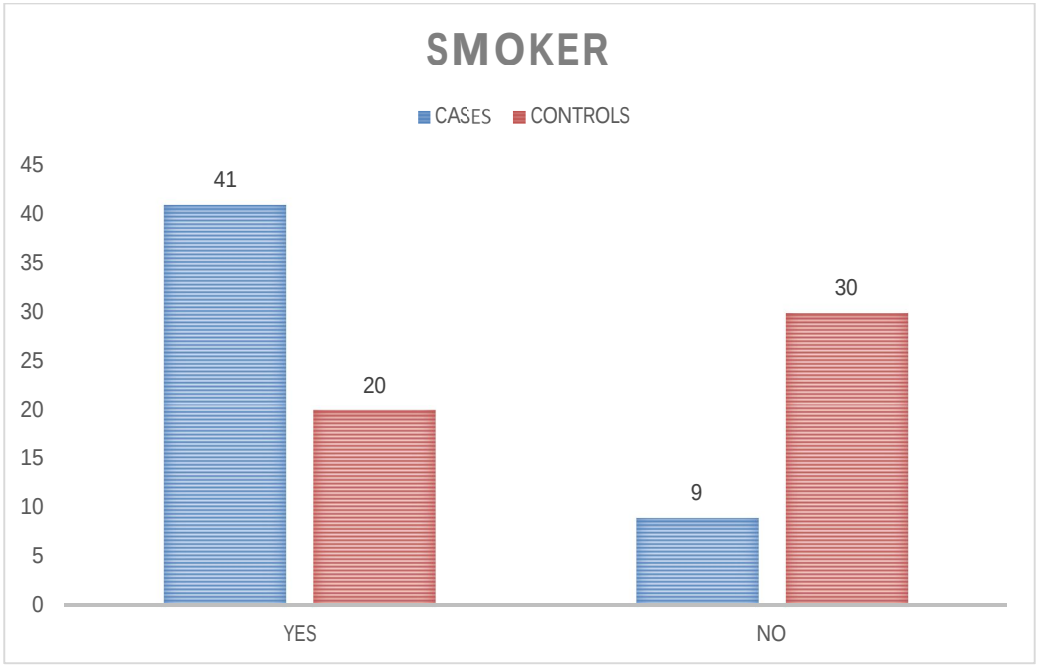
SMOKER	NO OF PATIENTS	PERCENTAGE
YES	61	61%
NO	39	39%

Table 12 Smoking Cases and Controls

SMOKER	PATIENTS	
	CASES	CONTROLS
YES	41	20
NO	9	30
P VALUE - 0.001		
ODDS RATIO - 6.83		
SIGNIFICANT		
CHI SQUARE TEST		



Graph 9 Smoking



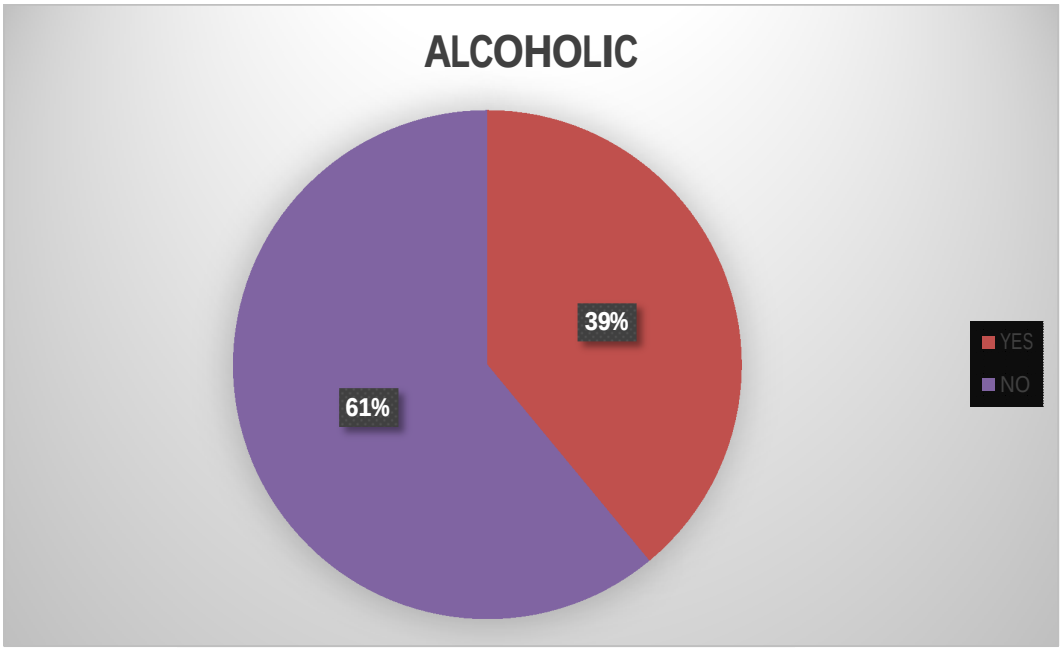
Graph10 Smoking Cases and Controls

Table 13 Alcoholism

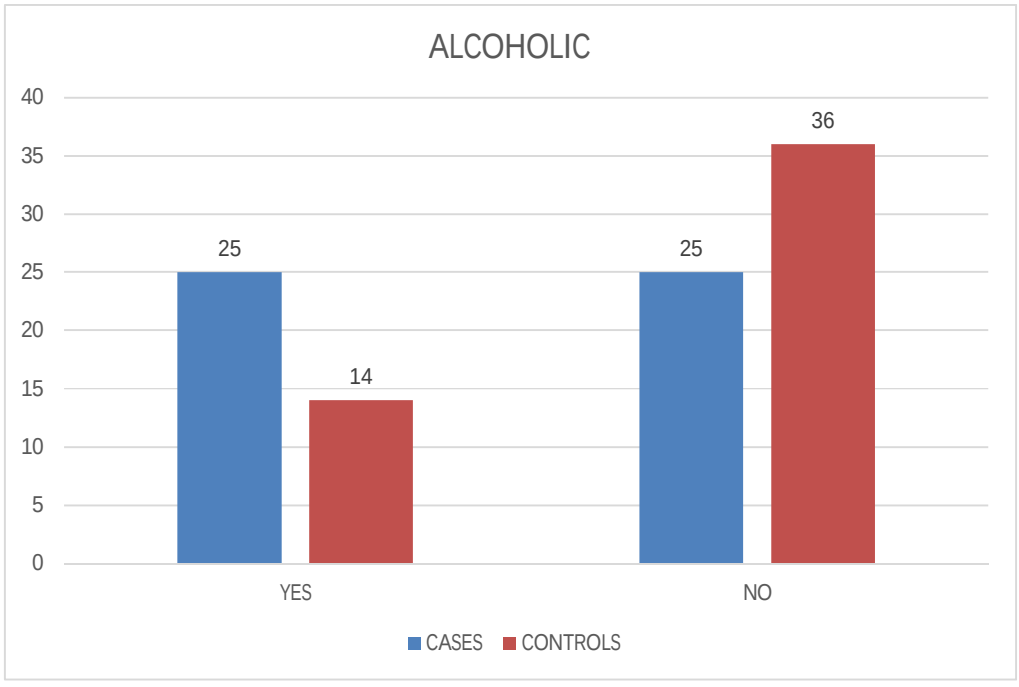
ALCOHOLIC	NO OF PATIENTS	PERCENTAGE
YES	39	39%
NO	61	61%

Table 14 Alcoholism Cases and Controls

ALCOHOLIC	PATIENTS	
	CASES	CONTROLS
YES	25	14
NO	25	36
P VALUE - 0.024		
ODDS RATIO - 2.57		
SIGNIFICANT		
CHI SQUARE TEST		



Graph 11 Alcoholism



Graph 12 Alcoholism Cases and Controls

Table 15 Demographic Characteristics (N=100)

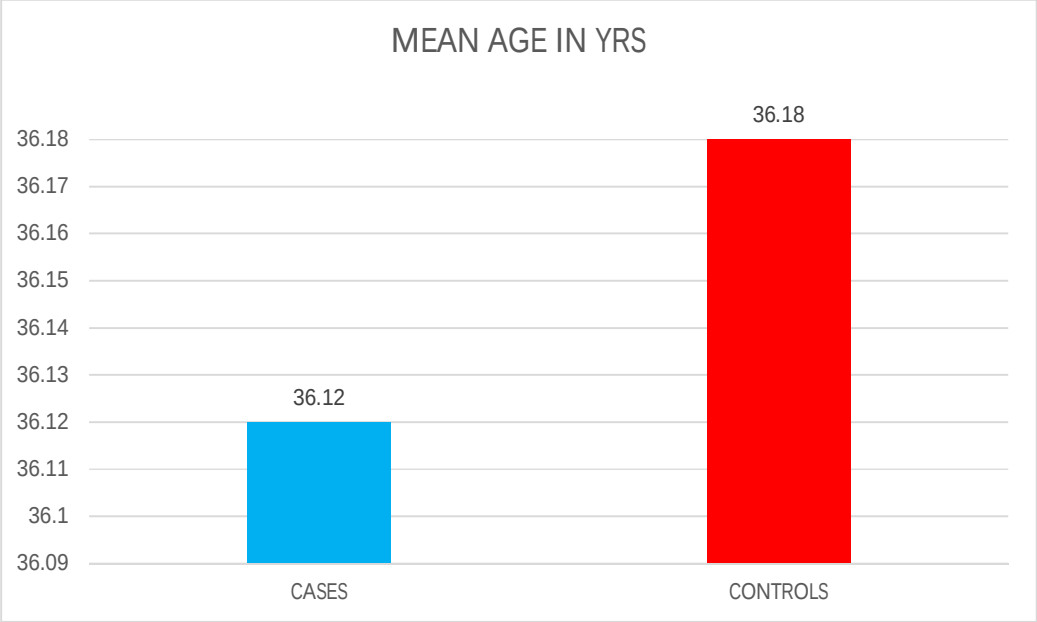
DEMOGRAPHIC CHARECTERISTICS (N=100)		
PARAMETER	**MEAN**	**SD**
AGE IN YEARS	36.15	2.4
BMI	25.79	2.28
TOTAL CHOLESTEROL	203.79	28.77
HDL	43.49	5.94
LDL	114.1	35.07
REMNANT COLESTEROL	48.96	18.69
TRIGLYCERIDES	193.7	64.78
NON-HDL	160.8	32.25
LDL/HDL RATIO	3.4	4.5
RC/HDL RATIO	1.25	0.82
TC/HDL RATIO	4.83	1.31

Table 16 Mean age Cases and Controls

PATIENTS	AGE IN YEARS	
	MEAN	SD
CASES	36.12	2.32
CONTROLS	36.18	2.49
P VALUE - 0.901		
NON SIGNIFICANT		
UNPAIRED T TEST		

Table 17 Body Mass Index

PATIENTS	BODY MASS INDEX	
	MEAN	SD
CASES	26.48	2.14
CONTROLS	25.1	2.24
P VALUE - 0.002		
SIGNIFICANT		
UNPAIRED T TEST		



Graph13 Mean age Cases and Controls

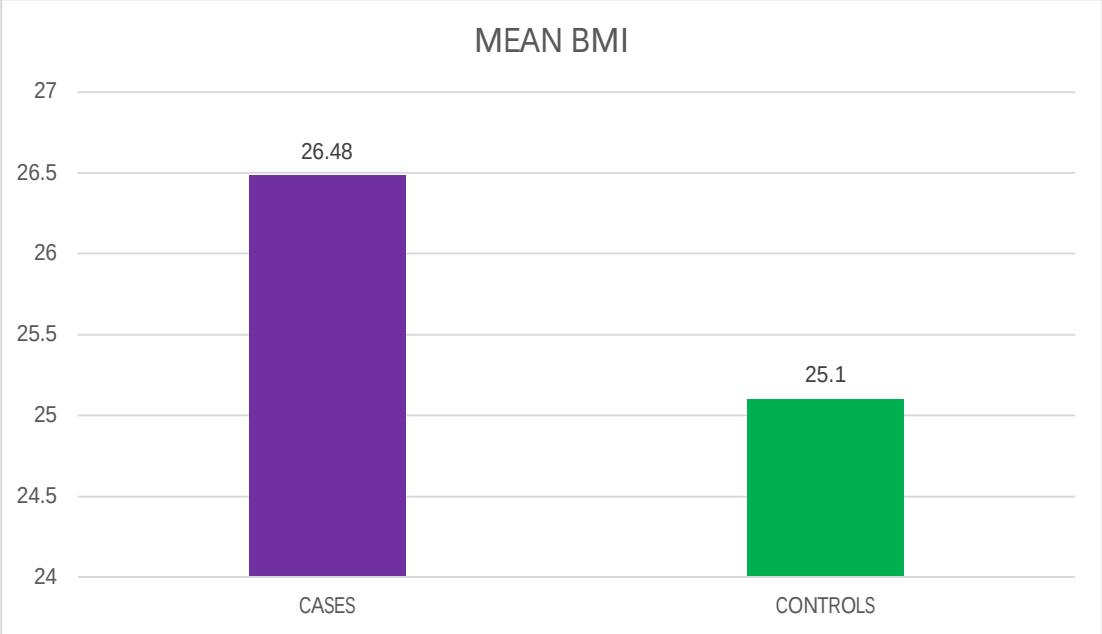


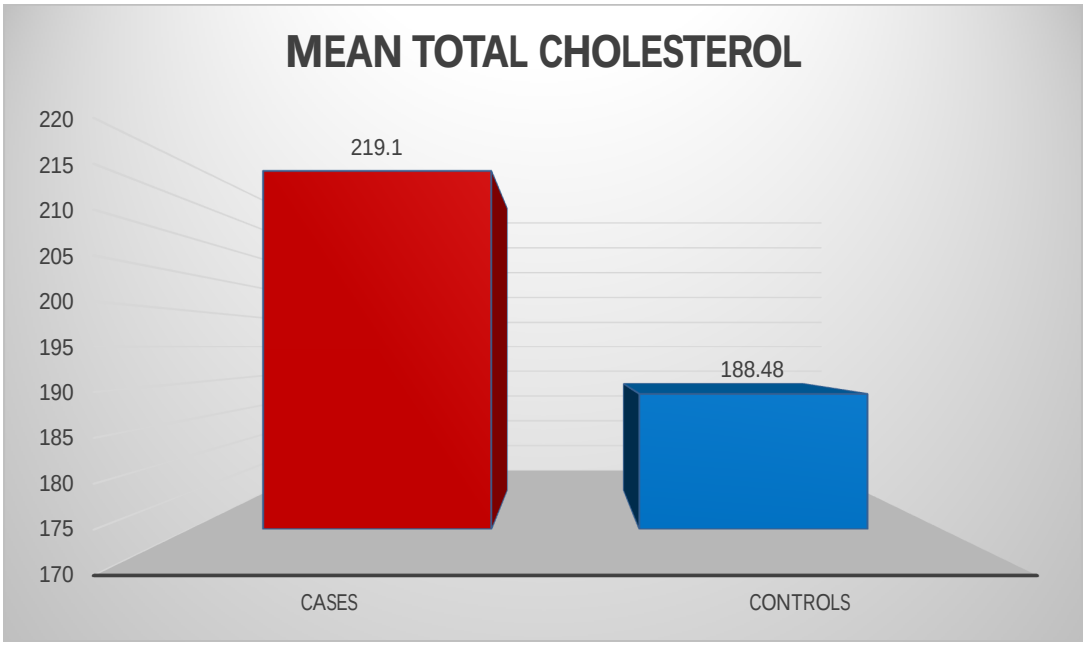
Table 14 Body Mass Index

Table 18 Total Cholesterol

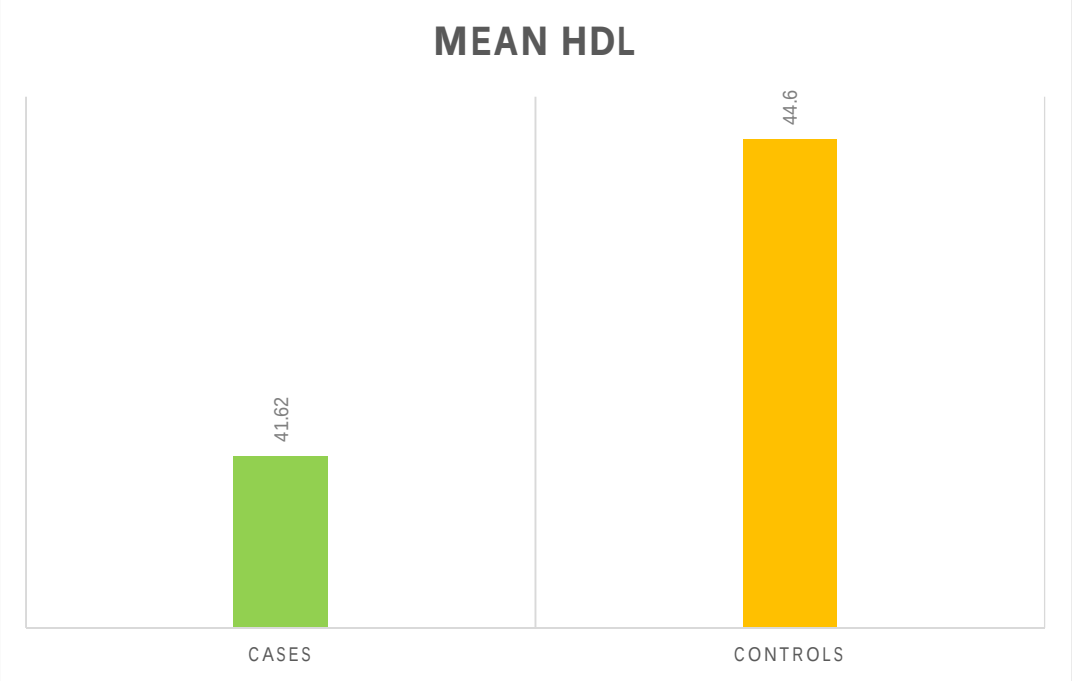
PATIENTS	TOTAL CHOLESTEROL	
	MEAN	SD
CASES	219.1	26.82
CONTROLS	188.48	21.8
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		

Table 19 High Density Lipoprotein

PATIENTS	**HIGH DENSITY LIPOPROTEIN**	
	MEAN	**SD**
CASES	41.62	6.23
CONTROLS	44.6	5.31
P VALUE - 0.031		
SIGNIFICANT		
UNPAIRED T TEST		



Graph 15 Total Cholesterol



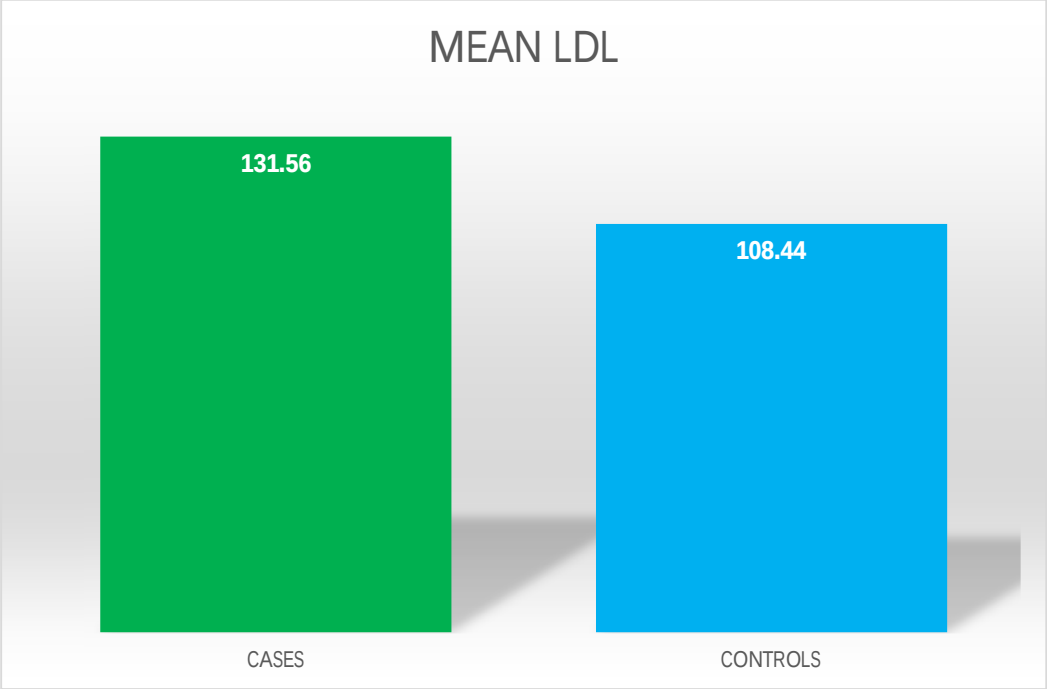
Graph 16 High Density Lipoprotein

Table 20 Low Density Lipoprotein

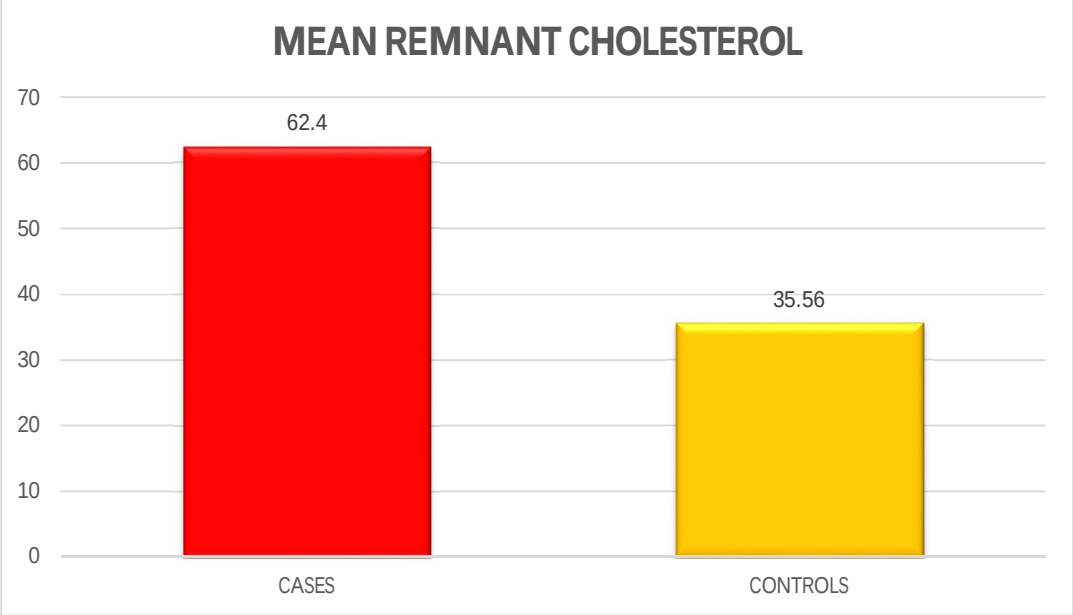
PATIENTS	LOW DENSITY LIPOPROTEIN	
	MEAN	**SD**
CASES	131.56	13.72
CONTROLS	108.44	17.94
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		

Table 21 Remnant Cholesterol

PATIENTS	REMNANT CHOLESTEROL	
	MEAN	**SD**
CASES	62.4	17.15
CONTROLS	35.56	6.68
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		



Graph 17 Low Density Lipoprotein



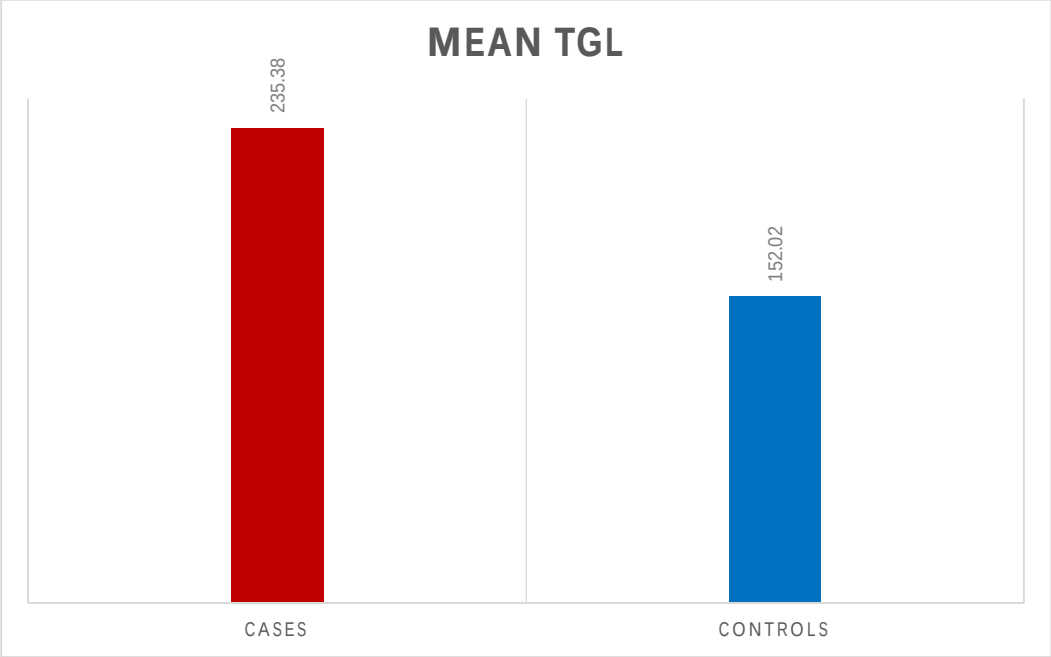
Graph 18 Remnant Cholesterol

Table 22 Triglycerides

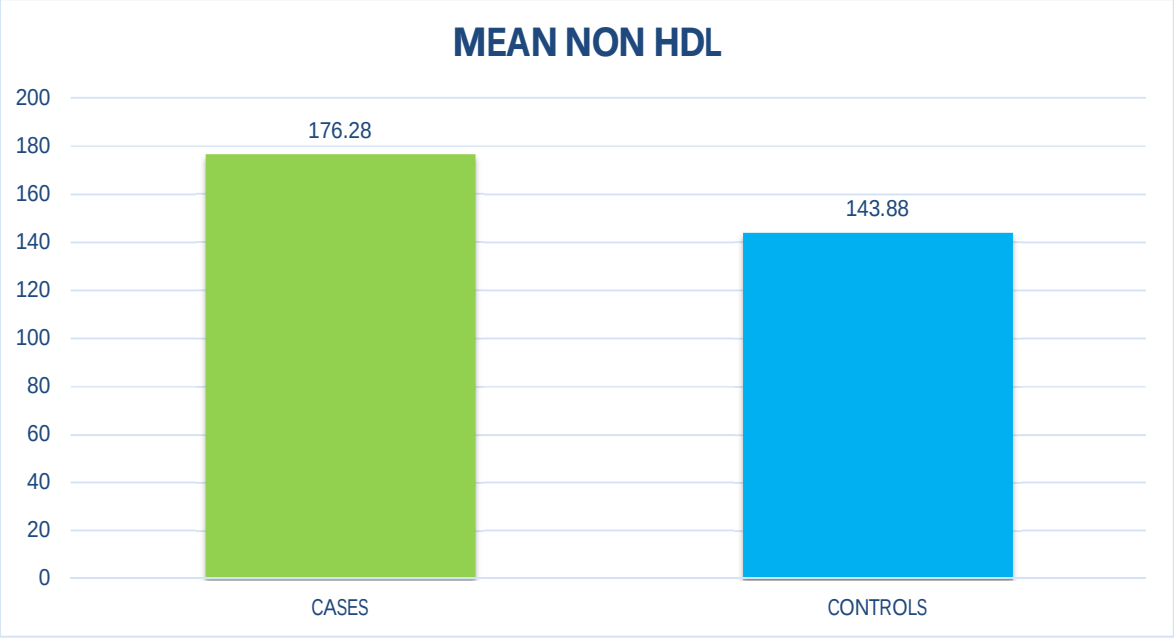
PATIENTS	TRIGLYCERIDES	
	MEAN	**SD**
CASES	235.38	53.47
CONTROLS	152.02	45.55
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		

Table 23 Non HDL Cholesterol

PATIENTS	NON HDL	
	MEAN	**SD**
CASES	176.28	31.86
CONTROLS	143.88	23.47
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		



Graph 19 Triglycerides



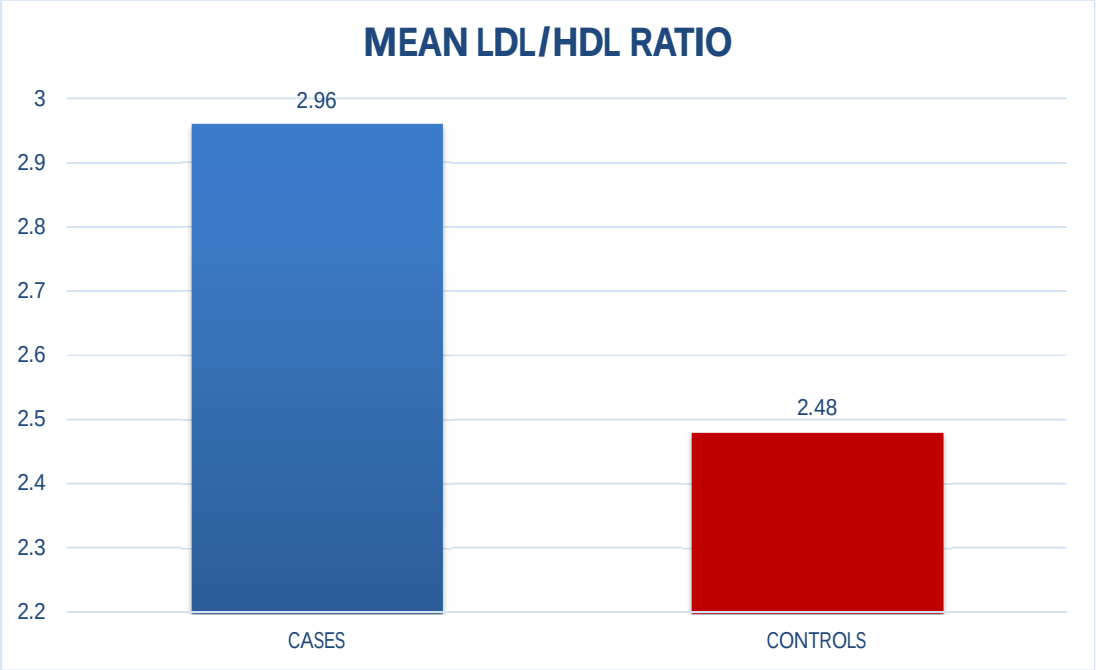
Graph 20 Non HDL Cholesterol

Table 24 LDL HDL Ratio

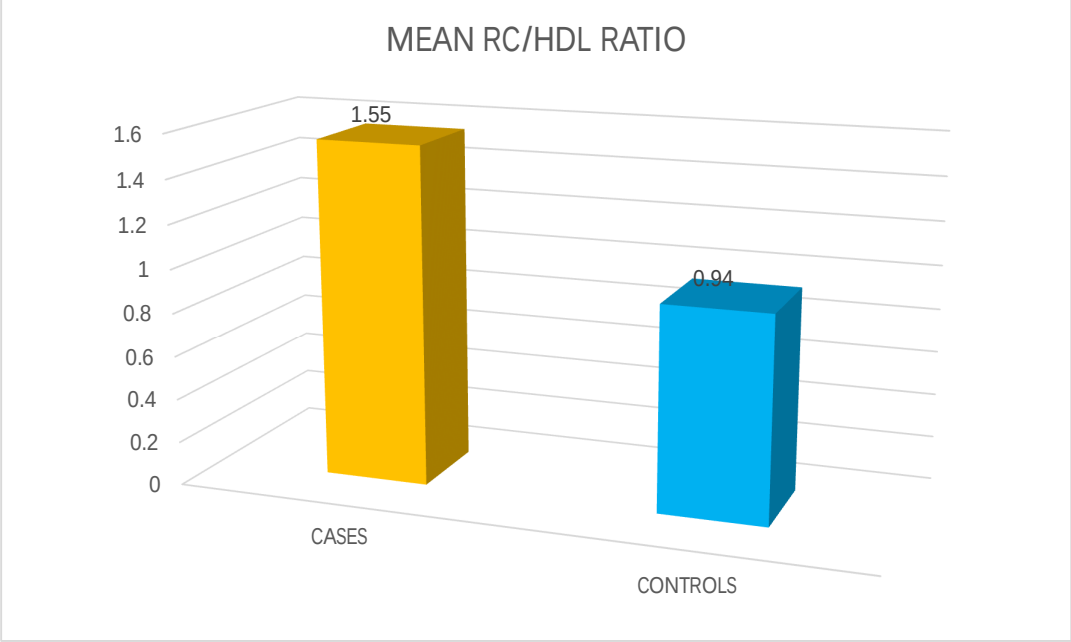
PATIENTS	LDL/HDL RATIO	
	MEAN	SD
CASES	2.96	0.42
CONTROLS	2.48	0.54
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		

+Table 25 RC HDL Ratio

PATIENTS	RC/HDL RATIO	
	MEAN	SD
CASES	1.55	0.65
CONTROLS	0.94	0.87
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		



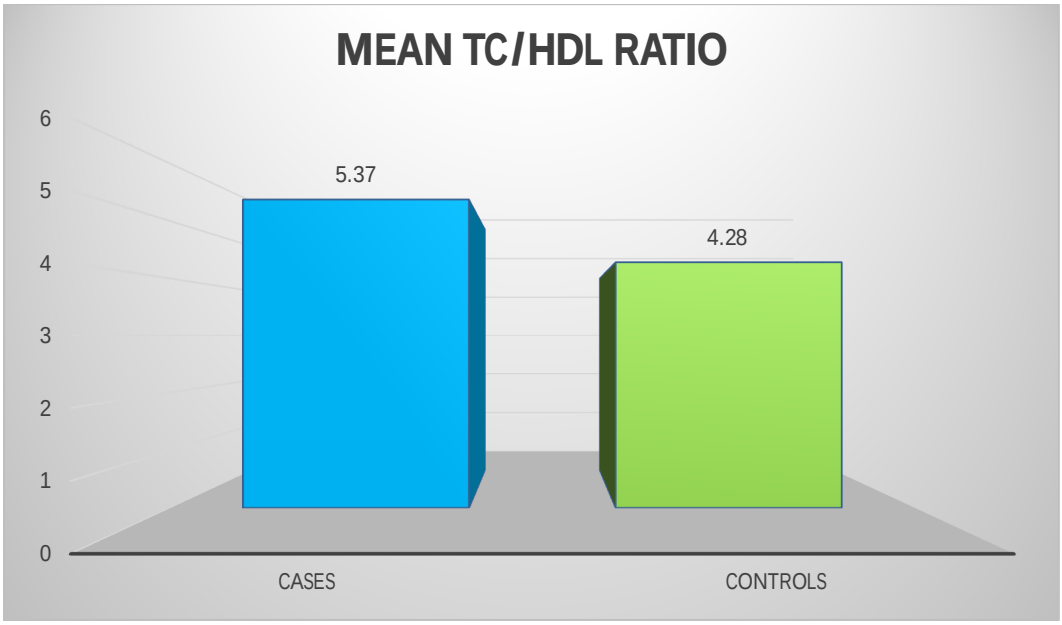
Graph 21 LDL HDL Ratio



Graph 22 RC HDL Ratio

Table 26 TC HDL Ratio

	TC/HDL RATIO	
PATIENTS	MEAN	SD
CASES	5.37	1.5
CONTROLS	4.28	0.77
P VALUE - 0.001		
SIGNIFICANT		
UNPAIRED T TEST		



Graph 23 TC HDL Ratio

DISCUSSION

Hundred patients (50 patients admitted for STEMI in Coimbatore Medical College ICCU of age group less than 40 years and 50 age and gender matched) were prospectively enrolled for the study .The duration of the study was 1 year. Mean age of the study group was 36.15 years and all of the patients and controls were male and 34% of the patients were below 35 years .Almost half of the cases had family history of myocardial infarction. Thirty percent of the cases had diabetes mellitus and was statistically not significant. Hypertension was present in 46% of the cases and 82% of the cases were smokers and was found to be statistically significant which was similar to the results in the study by Goliasch et al.50% of the cases were alcoholic and was statistically significant.

The mean BMI of the cases and controls were 26.48and 24.1 with SD of 2.14 and 2.24 and was statistically significant with a P value of 0.002. The total cholesterol of the cases and controls were 26.48and 24.1 with SD of 2.14 and 2.24 and was statistically significant with a P value of 0.002.The mean total cholesterol was 219mg/dl among patients compared to 188.4 among controls and had significant statistical significance with a P value of 0.001.The mean HDL and LDL among patients was 41.62 and 131.56 compared to 44.6 and 108.44 of that of controls and both these parameters were statistically significant .The mean triglyceride among cases was significantly high compared to

controls throwing light to the increased incidence hypertriglyceridemia among patients with young myocardial infarction and had a P value of 0.001.the remnant cholesterol levels calculated as total cholesterol minus HDL cholesterol minus LDL cholesterol. The mean remnant cholesterol among cases was 62.4mg/dl and that of controls were 35.6mg/dl .The levels were approximately two times higher in patients when compared to controls and was significant statistically with a p value of 0.001.The non HDL fraction was calculated by subtracting HDL levels from the total cholesterol levels and was significant statistically .The cholesterol ratios like LDL HDL ratio RC to HDL ratio and Total cholesterol to HDL ratio all showed significant statistical correlation all with a P value of 0.001.

Previous studies about remnant cholesterol done by Jorgensen AB et al , Nordestgaard BG et al showed there is a significant association with remnant cholesterol and atherosclerosis . Studies by Varbo et al demonstrated that elevated remnant cholesterol levels show that an increment of 1 mmol/L (39 mg/dL) in levels of nonfasting remnant cholesterol associates with a 2.8-fold increased risk of IHD, independently of high-density lipoprotein cholesterol levels. Present study also shows almost a mean increase of 26.8 mg/dl of remnant cholesterol among cases of young myocardial infarction confirming the role of elevated remnant cholesterol as a risk factor.

SUMMARY

Remnant cholesterol is the non HDL LDL fraction of cholesterol fraction .The study was conducted during a time span of 1 year among 50 patients who were admitted for STEMI of age less than 50 years as cases and 50 age and sex matched individuals attending OPD of the department as controls .All of the patients were male and one third of the cases were under the age group of less than35 years of age .Family history of myocardial infarction showed no statistical significance in the study. History of smoking alcohol intake diabetes and hypertension was significant as risk factors in young myocardial infarction patients .All cholesterol fractions showed statistically significant P value especially the triglycerides and showed the underlying dyslipidemic component acting as the trigger in premature MI..The mean remnant cholesterol was 62.4mg/dl in cases and 35.6mg/dl among controls and showed statistical significance .The non HDL cholesterol fraction also showed significance .Various cholesterol ratios like LDL : HDL,RC :HDL,TC:HDL also were found to be significant .The risk factor profile in young myocardial infarction patients with special focus on lipid parameters is very much important

CONCLUSION

The risk factor profile of young patients with myocardial infarction is different compared to elderly individuals .There is an accelerated atherosclerosis which is contributed by a higher incidence of smoking, alcoholism diabetes and hypertension. As lipids and its components also have a significant role in atherosclerosis the evaluation of lipid parameters in detail in such patients is very important not only in aggressively treating the patients but also in screening the family members .The family screening and identification of related individuals is very important in preventing atherosclerosis related future events .

Remnant cholesterol is the non HDL LDL fraction and has a significant association with premature myocardial infarction .The level of remnant cholesterol can be calculated from a lipid profile and do not need a separate estimation.

LIMITATIONS

The case–control study design, where measurements are obtained after the outcome of interest has already occurred. No information available on the impact of the acute phase of myocardial infarction on remnant cholesterol.

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ANNEXURE-1

PROFORMA

NAME:-

AGE :-

SEX :-

ADRESS:-

FAMILY HISTORY OF MYOCARDIAL INFARCTION :-

DIABETES MELLITUS:-

SYSTEMIC HYPERTENSION:-

SMOKING:-

ALCOHOLISM:-

HEIGHT:-

WEIGHT:-

BMI:-

TOTAL CHOLESTEROL:-

HDL CHOLESTEROL :-

LDL CHOLESTEROL:-

TRIGLYCERIDES:-

ANNEXURE -2

CONSENT FORM

Statement of Consent

I, _____, do hereby volunteer and consent to participate in this study being conducted by Dr. NITHIN K titled *Remnant Cholesterol As A Risk Factor For Myocardial Infarction In Age Group Less Than 40 Years*. I have read and understood the consent form (or) it has been read and explained to me thoroughly. I am fully aware of the study details as well as aware that I may ask questions to him at any time.

Signature / Left Thumb Impression of the patient

Station: Coimbatore

Date:

Signature / Left Thumb Impression and Name of the witness

Station: Coimbatore

Date:

ஒப்புதல் படிவம்

பெயர் :

வயது :

பாலினம் :

முகவரி:

கோவை அரசு மருத்துவக்கல்லூரி மருத்துவமனையில் மருத்துவர். **nf. ejjid;** தலைமையில் நடைபெறும் இந்த ஆய்வில் முழு சம்மதத்துடன் கலந்துகொள்ள சம்மதிக்கிறேன். இந்த ஆய்வில் என்னை பற்றி விவரங்களை பாதுகாப்புடன் இந்த ஆய்வில் வெளியிட ஆட்சேபணை இல்லை என்று தெரிவித்துக் கொள்கிறேன் .எந்த நேரத்திலும் ஆய்வில் இருந்து எந்த நேரத்திலும் விலக்கிக்கொள்ளும் உரிமை உண்டு என்று அறிவேன் .

இடம் :

தேதி:

கைகெயாப்பம்
/ரேகை

ANNEXURE-3

KEY TO MASTER CHART

SEX

1-MALE

2-FEMALE

FAMILY H/O MI

1-PRESENT

2-ABSENT

DIABETES

1-PRESENT

2-ABSENT

HYPERTENSION

1-PRESENT

2-ABSENT

SMOKING

1-SMOKER

2-NON SMOKER

ALCOHOLIC

1-ALCOHOLIC

2- NON ALCOHOLIC

MASTER CHART - CASES

S.No	NAME	AGE	SEX	FAMILY H/O MI	DIABETES	HYPERTENSION	SMOKER	ALCOHOLISM	BMI	T CHOLESTEROL	HDL	LDL	REMNANT CHOLESTEROL	TRIGLYCERIDES	NON HDL	LDL/HDL RATIO	RC/HDL RATIO	TC/HDL RATIO
1	Krishnamoorthi	38	1	2	1	1	1	1	25	186	50	98	38	156	136	2	0.8	3.7
2	Srinivasan	36	1	1	1	2	1	2	26	210	51	98	61	221	159	1.9	1.2	4.1
3	Palani	35	1	1	1	2	1	2	26	225	39	111	75	259	186	2.8	2.1	5.8
4	Suresh Babu	39	1	1	1	1	1	1	30	268	32	146	90	294	236	4.5	2.8	8.3
5	Shanmugam	38	1	2	2	2	1	1	25	218	51	103	64	227	167	2	1.3	4.3
6	Jayapal	35	1	1	2	2	1	1	25	199	49	99	51	239	150	2	1	4.1
7	Karhikeyan	36	1	1	2	2	1	2	25	185	51	97	37	199	134	1.9	0.8	3.6
8	Santhosh	38	1	1	2	1	1	2	26	209	49	100	60	218	160	2	1.2	4.3
9	Radhakrishnan	35	1	2	2	2	2	2	26	203	45	104	54	236	158	2.3	1.2	4.5
10	Subramnaniam	38	1	1	2	1	2	2	25	224	40	122	62	246	184	3.1	1.6	5.6
11	Ganesan	39	1	1	2	1	1	1	30	269	35	145	89	318	234	4.1	2.5	7.7
12	Manikkan	36	1	1	1	1	2	2	28	225	37	123	65	247	188	3.3	1.8	6
13	Venkatesan	38	1	1	2	2	1	1	28	228	38	126	64	248	190	3.3	1.7	6

14	Muthukumar	35	1	2	2	1	2	2	25	181	47	101	33	189	134	2.1	0.7	3.9
15	Manikkan	34	1	2	2	2	1	1	28	219	44	116	59	221	175	2.6	1.3	5
16	John	39	1	1	1	1	1	2	28	230	34	130	66	252	196	3.8	1.9	6.8
17	Manikkan	39	1	1	1	2	1	1	30	271	33	417	91	328	238	4.4	2.7	8.2
18	Parthasarathi	36	1	2	2	2	1	1	28	223	41	121	63	245	184	3	1.5	5.4
19	Kathirvel	34	1	1	2	1	1	1	25	213	52	97	64	224	161	1.9	1.2	4.1
20	Magesh	35	1	2	2	2	1	2	26	210	45	104	61	223	165	2.3	1.4	4.7
21	Jeevanandam	39	1	1	1	1	1	2	30	271	31	149	91	318	240	4.8	2.9	8.7
22	Dhinesh	36	1	2	1	1	1	1	25	214	48	103	63	229	166	2.1	1.3	4.5
23	Arul Das	37	1	2	1	2	2	2	28	227	39	108	80	254	188	2.8	2.1	5.8
24	Nagaraj	33	1	2	2	1	1	2	24	189	52	96	41	227	137	1.8	0.8	3.6
25	Elangovan	36	1	1	2	2	1	2	26	208	44	105	59	219	164	2.4	1.3	4.7
26	Ravichandran	38	1	1	1	2	1	1	28	224	43	109	72	259	181	2.5	1.7	5.2
27	Surya	39	1	1	1	1	2	1	29	268	31	150	87	329	237	4.8	2.8	8.6
28	Kannan	35	1	1	2	2	1	2	26	221	39	112	70	236	182	2.9	1.8	5.7
29	Ahamed	36	1	2	2	2	1	1	25	204	41	108	55	227	163	2.6	1.3	4.9
30	Rajendran	37	1	1	2	1	1	1	27	220	42	118	60	238	160	2.8	1.4	5.2
31	Jothiswaran	33	1	2	2	1	1	1	23	178	49	98	31	162	129	2	0.6	3.6
32	Selvam	38	1	1	2	2	1	2	28	225	41	121	63	245	184	3	1.5	5.5

33	Raman	32	1	2	2	1	1	1	26	218	44	116	58	236	174	2.6	1.3	5
34	Eswaran	39	1	1	1	2	1	2	30	274	31	149	94	332	243	4.8	3	8.8
35	Moideen	37	1	1	2	1	1	2	27	217	45	115	57	219	172	2.6	1.3	4.8
36	Manivannan	34	1	2	2	2	1	2	27	216	46	114	56	324	170	2.5	1.2	4.7
37	Rangaraj	34	1	2	2	2	1	2	22	175	48	99	28	158	127	2.1	0.6	3.6
38	PaulRaj	39	1	1	1	2	1	1	29	277	31	149	97	340	240	4.8	3.1	8.9
39	Balamurugan	37	1	2	2	2	2	2	24	221	39	121	61	227	182	3.1	1.6	5.7
40	Arun Kumar	34	1	2	2	2	2	1	22	171	41	106	24	152	130	2.6	0.6	4.2
41	Vijay	38	1	2	1	1	1	1	23	191	52	96	43	240	139	1.8	0.8	3.7
42	Sekar	29	1	2	2	2	1	2	27	206	35	104	67	236	171	3	1.9	5.9
43	Gopal	34	1	2	2	1	1	2	27	217	42	105	70	236	175	2.5	1.7	5.2
44	Ajay Kumar	39	1	1	2	1	1	1	29	265	37	143	85	29	228	3.8	2.3	7.2
45	Raghu	37	1	2	2	2	1	1	24	209	46	102	61	221	163	2.2	1.3	4.5
46	Samuel	31	1	2	2	1	2	2	23	196	46	102	48	227	150	2.2	1	4.3
47	Paramasivam	34	1	2	2	2	1	2	29	216	50	103	63	228	166	2.1	1.3	4.3
48	Saravana Kumar	37	1	2	2	1	1	1	27	207	39	110	58	218	168	2.8	1.5	5.3
49	Prabakaran	34	1	2	2	2	1	1	27	215	47	108	60	219	168	2.3	1.3	4.6
50	Saleem	37	1	1	2	1	1	1	27	219	37	111	71	194	182	3	1.9	5.9

MASTER CHART – CONTROLS

S.No	NAME	AGE	SEX	FAMILY H/O MI	DIABETES	HYPERTENSION	SMOKER	ALCOHOLISM	BMI	T CHOLESTEROL	HDL	LDL	REMNANT CHOLESTEROL	TRIGLYCERIDES	NON HDL	LDL/HDL RATIO	RC/HDL RATIO	TC/HDL RATIO
1	Ravi	38	1	1	2	2	2	1	24	189	46	107	36	152	143	2.3	0.8	4.1
2	Paramasivan	35	1	2	1	2	1	2	21	231	35	144	52	247	196	4.1	1.5	6.6
3	Peter	29	1	2	2	1	2	1	28	217	43	137	37	191	174	3.2	0.8	5
4	Sarathi	36	1	1	2	2	1	2	24	188	45	108	35	154	143	24	0.8	4.1
5	Muruganandan	39	1	2	2	2	2	2	25	149	56	72	27	69	93	1.3	0.4	2.7
6	Sivaprakasam	37	1	1	2	2	1	1	21	159	42	79	38	74	117	1.9	0.9	3.8
7	Nirmal	29	1	1	2	2	2	2	25	187	44	109	34	157	143	2.5	0.8	4.3
8	Nandhakumar	37	1	2	1	2	2	2	29	229	39	141	49	240	190	3.6	1.3	5.9
9	Balaji	39	1	1	2	2	1	1	24	188	42	107	39	169	146	2.5	0.9	4.5
10	Selvraj	35	1	2	2	2	2	2	27	186	43	110	33	151	143	2.6	0.8	4.3
11	Rajan	31	1	2	2	2	1	1	27	151	54	74	23	71	97	1.4	0.4	2.8
12	Rajagopal	37	1	2	2	2	2	2	27	191	45	112	34	171	146	2.5	0.8	4.2
13	Pradeep	36	1	2	2	1	1	2	25	185	51	102	32	149	134	2	0.6	3.6
14	Marimuthu	38	1	2	1	2	2	1	21	225	41	138	46	222	184	3.4	1.1	5.5

15	Muthu	32	1	1	2	2	2	2	25	186	48	105	33	152	138	2.2	0.7	3.9
16	Gowtham	37	1	1	2	2	1	2	28	184	52	101	31	146	132	1.9	0.6	3.5
17	Gukan	39	1	2	2	2	2	2	24	152	50	78	24	76	102	1.6	0.5	3
18	Manogaran	35	1	2	2	1	1	2	27	194	47	115	32	174	147	2.4	0.7	4.1
19	Vignesh Kumar	32	1	1	2	2	2	1	21	190	43	110	37	154	147	2.6	0.9	4.4
20	Manikkam	37	1	2	2	2	1	2	29	223	41	134	48	209	182	3.3	1.2	5.4
21	Chandran	39	1	2	2	2	2	1	25	180	50	99	31	169	130	2	0.6	3.6
22	Thomas	36	1	1	2	2	1	2	26	191	41	112	38	157	150	2.7	1	4.7
23	Shamraj	33	1	2	2	2	2	2	23	154	48	80	26	78	106	1.7	0.5	3
24	Uthayakumar	39	1	2	2	1	1	2	26	190	51	109	30	159	139	2.1	0.6	3.7
25	Vanaraj	36	1	1	2	2	2	2	22	192	42	111	39	159	150	2.6	0.9	4.6
26	Chandrasekhar	39	1	1	1	2	2	2	29	218	42	133	43	202	176	32	1	5.2
27	Senthil Prabhu	39	1	2	2	2	2	1	24	186	48	102	36	157	138	2.1	0.8	3.9
28	Prasanth	35	1	1	2	1	1	2	26	193	41	112	40	161	152	2.7	1	4.7
29	Biju	34	1	2	2	2	2	2	25	155	48	82	25	79	107	1.7	0.5	3.2
30	Sathyaraj	39	1	2	2	2	2	2	22	188	46	107	35	161	142	2.3	6.8	4.1
31	Peter	36	1	1	2	2	1	1	26	194	41	112	41	163	153	2.7	1	4.7
32	Sathish Kumar	38	1	1	1	2	2	2	27	221	45	130	46	206	176	29	1	4.9
33	Rooban	34	1	2	2	2	1	2	26	185	46	106	33	150	139	2.3	0.7	4
34	Vimal	39	1	2	2	1	2	2	26	195	40	113	42	161	155	2.8	1.1	4.9
35	Murali	36	1	1	2	2	1	1	22	152	39	86	27	76	113	2.2	0.7	3.9

36	Mahalingam	38	1	1	2	2	2	2	24	181	36	107	38	163	145	3	1.1	5
37	Subramanian	34	1	2	2	2	2	2	23	197	62	116	19	167	135	1.9	0.4	3.1
38	Dhanaraj	37	1	2	2	1	1	2	28	213	45	128	40	199	168	2.8	0.9	4.7
39	Muralidhran	37	1	2	2	2	2	1	26	187	44	107	36	164	143	2.4	0.8	4.3
40	Nithish	35	1	1	1	2	2	2	28	222	48	139	35	188	174	2.9	0.7	4.6
41	Manoj	38	1	2	2	2	2	2	26	188	42	108	38	161	146	2.6	0.9	4.5
42	Shakthivel	34	1	1	2	2	1	2	27	194	46	114	34	117	148	2.5	0.7	4.2
43	Sikandar	37	1	2	2	2	2	2	25	156	44	76	36	71	112	1.7	0.8	3.5
44	Harikrishnan	36	1	2	2	1	2	2	22	209	43	124	42	204	166	2.9	1	4.9
45	Ayyapan	36	1	2	2	2	1	1	27	188	44	109	35	150	144	2.5	0.8	4.3
46	Justin	37	1	2	2	2	2	2	25	156	35	91	30	79	121	2.6	0.9	4.5
47	Rajkumar	38	1	2	2	2	2	2	23	183	46	102	35	147	137	2.2	0.8	4
48	Vasanth	38	1	1	2	1	1	2	27	206	45	121	40	189	161	2.7	0.9	4.6
49	Asok Kumar	36	1	2	2	2	2	1	24	184	42	106	36	152	142	2.5	0.9	4.4
50	Prabhu	38	1	2	2	2	1	2	23	162	33	97	32	84	129	2.9	1	4.9